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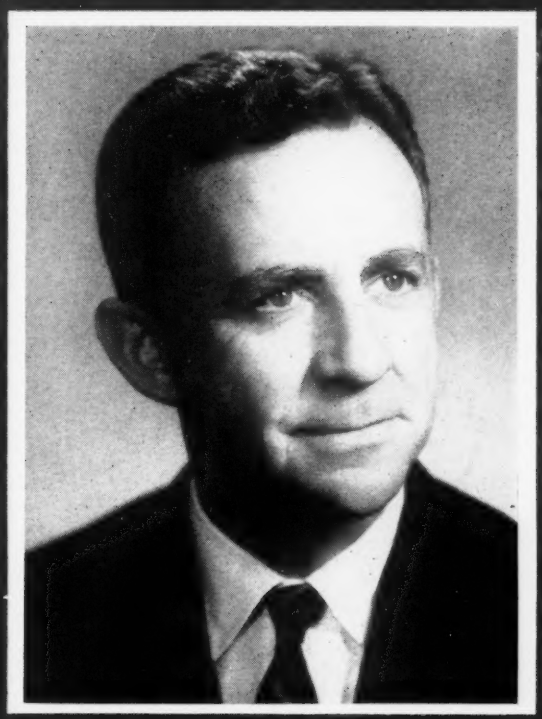

WALTER E. BROWN, M.D., President
Oklahoma State Medical Association

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Editorial

The Continuous Education of A Physician

"The want of energy is one of the main reasons why so few persons continue to improve in later years. They have not the will, and do not know the way. They 'never try an experiment' or look up a point of interest for themselves; they make no sacrifices for the sake of knowledge; their minds, like their bodies, at a certain age become fixed."

Jowett's Introductions to Plato.

This quotation formed the theme for Sir William Osler's lecture on the Educational Value of the Medical Society![1] I would like to quote several passages from that lecture:

"There are many problems and difficulties in the education of a medical student, but they are not more difficult than the question of the continuous education of the general practitioner. Over the one we have some control, over the other, none. The Universities and the state board make it certain that one has a minimum, at least, of professional knowledge, but who can be certain of the state of that knowledge of the other in five or ten years from the date of graduation?

"No class of men needs to call to mind more often the wise comment of Plato that education is a life-long business . . . The more serious problem relates to the education of the practitioner after he has left the schools. The foundations may not have been laid upon which to erect an intellectual structure, and too often the man starts with a total misconception of the prolonged struggle necessary to keep the education he has, to say nothing of bettering the instruction of the schools. As the practice of medicine is not a business and can never be one, the education of the heart—the moral side of the man—must keep pace with the education of the head . . . The doctor's post-graduate education comes from patients, from books and journals, and from societies, which should be supplemented every five or six years by a return to a post-graduate school to get rid of an almost inevitable slovenliness in methods of work."

Osler, in this lecture, was concerned primarily with the educational value of the medical society. Most specialty societies and national societies have continued with education of the members as the primary objective. The same cannot be said about many county medical societies.[2] In this group, affairs of the business of medicine are consuming a greater portion of the time and effort and matters of education of the members, a smaller portion.

Today, with this change in local medical societies, I am certain that Sir William Osler would suggest returning to a postgraduate school more often than once every five or six years. Indeed, most physicians in Oklahoma participate in postgraduate programs more frequently than this. A review of the records of the University of Oklahoma Postgraduate office is of some interest. During the year 1958-1959 there were 20 courses offered. The courses included Internal Medicine, Surgery, Pediatrics, Obstetrics, Orthopedics and many other subspecialties. Thirty-eight guest lecturers from other states served as instructors in addition to the local faculty. A total of 1,190 physicians attended one or more courses. The distribution of these physicians by residence is as follows:

Oklahoma County	429
Tulsa County	77
Other Oklahoma Counties	325
Out-of-State	309

One man attended 13 courses! A substantial number attended two or more courses. It would be anticipated that a large number of Oklahoma County physicians would attend, but the 375 attending from counties other than Oklahoma and Tulsa represents over 40 per cent of the practicing physicians. The growth of the program is indicated by the figures for 1949-50 compared with 1958-59.

	Physicians Attending Postgraduate Courses		
Year	Total Physicians	Out-of-State Physicians	
1949-50	211	14	
1952-53	247	27	
1958-59	1,190	309	

The figures for 1952-53 are included since at about this time the development of full-time teachers in the clinical departments had its beginnings and associated with this there was renewed interest in the continuing education of physicians.

The future development of the postgraduate program poses many questions.

The first is, should the postgraduate effort be one of continuing or reparative education? In other words, should the emphasis be on courses designed for the physician who has made a continued effort to educate himself, or should the courses be designed for the physician who has fallen shamefully behind in his education. The position of the American Medical Association Council on Medical Education and Hospitals is that the emphasis should be on continuing education.[3]

Should the subject be more basic or more practical?[2] Those that have advocated more practical to me, when queried as to what they meant by more practical, have invariably indicated more therapeutic. If a sound understanding of fundamentals is important and if concepts change as new methods become available, e.g., the development in understanding hemoglobinopathies with advent of electrophoretic techniques, then whose job is it to present these advances in fundamental knowledge? The University would seem to me to be remiss if it shirked this duty.

What method of presentation should be employed?[2] At the present, the lecture system is used almost exclusively. It is easier and cheaper but has few other advantages. Can seminars be incorporated into the program? The consecutive case conference has had wide application in the field of pulmonary disease.[4] In these conferences, each hospital participating presents 10 consecutive cases in some category, e.g., 10 consecutive cases admitted for tuberculosis. Usually two guest participants then criticize and discuss the cases. Could this method be applied for other subjects?

Where should courses be located?[2] The program of the University has been handicapped by an abominably poor auditorium with poor acoustics, uncomfortable seats and in general a rather barn-like atmosphere. Fortunately plans are underway to construct a new auditorium exclusively for the use of the postgraduate division. Should the courses all be given at the University of Oklahoma Medical School, or should some or all be given at other places in the State?[2,5] If so, where and how often? If this is done, can we induce the recalcitrant to drink in the educational pool, or will we still be satisfying only the thirsty?

How should the courses be financed?[2] If this is entirely by tuition, would physicians be willing to pay the cost or would attendance lag? Should the courses be financed by appropriated funds from the State Legislature? Should medical societies participate in the financing? Some do now, e.g., Oklahoma City Internists Association, Oklahoma Chapter of the American College of Surgeons, Oklahoma City Surgical Society, Oklahoma Association of Radiologists, Oklahoma Association of Pathologists, Oklahoma City Pediatrics Society, Oklahoma City Academy of Ophthalmology and Otolaryngology, Oklahoma Obstetrical and Gynecological Society, and others. Should county medical societies and the State Medical Association help support the program at the University? Should the volunteer health agencies help support courses for physicians? The Oklahoma Heart Association, Oklahoma Tuberculosis Association, American Cancer Society and others do this now. Should pharmaceutical firms help support the program as they have in the past?

The answers to all of these questions require thoughtful consideration and subsequent experimentation.[2] Many will remain only partially answered. Your suggestions and criticisms are welcomed by the postgraduate office. I would submit that your criticism should be based on evidence. Recently a physician was critical of the postgraduate program at the University. On inquiry it developed that he had not attended a course in six years!

The University and the physicians in the State, working together, can develop a program that will serve the needs for continuing education of physicians.—*J.F.H.*

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Fluid, Electrolyte and Nutritional Balance

The
First Oklahoma Colloquy
on
Advances in Medicine

Edited by

JAMES F. HAMMARSTEN, M.D.
Associate Professor of Medicine
University of Oklahoma School of Medicine and
Chief, Medical Service
Veterans Administration Hospital
Oklahoma City, Oklahoma

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Introduction

Stewart G. Wolf, Jr., M.D.

FOR THE FIRST Oklahoma Colloquy we have selected a topic which is at once intricate and broad. It is one in which the large amount of current experimental activity has not been adequately interpreted to the medical public. Since the concepts are difficult to grasp for those with a medical school background of fifteen or more years ago, we have selected the essayists for their articulateness as well as their stature in the field. With the aid of this distinguished group, we are attempting to make a badly needed contribution to post graduate education instead of a didactic review of the subject at hand. The men who are doing the work have presented their data in a comprehensive way but without attempting to cover the field. The questions and discussions from the audience and vigorous interchanges among the essayists themselves which are stimulated have been recorded. The flavor was that of a research meeting without its esoteric, fragmentary and highly specialized character. We are grateful to Baxter Laboratories for providing the financial support that made this Colloquy possible, and to the *Journal* of the Oklahoma State Medical Association for its publication and especially for making the entire Colloquy available for reference in a single issue of the *Journal*.

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Participants

ARNOLD S. RELMAN, M.D.—Associate Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts

ROBERT E. COOKE, M.D.—Professor of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland

BEN I. HELLER, M.D.—Professor of Medicine, University of Arkansas, Little Rock, Arkansas

WILLIAM E. ABBOTT, M.D.—Associate Professor of Surgery, Western Reserve University, Cleveland, Ohio

CURTIS P. ARTZ, M.D.—Associate Professor of Surgery, University of Mississippi, Jackson, Mississippi

ROBERT TARAIL, M.D.—Metabolic Section, Roswell Park Memorial Institute, Buffalo, New York

J. U. SCHLEGEL, M.D.—Director, Urological Research Laboratory, Assistant Professor, Urological Surgery, University of Rochester, Rochester, New York. Presently Professor of Urology, Head of Division of Urology, Department of Surgery, Tulane University School of Medicine, New Orleans, Louisiana

JOHN H. BLAND, M.D., Associate Professor of Medicine, University of Vermont Medical School, Burlington, Vermont

WILLIAM W. SCHOTTSTAEDT, M.D.—Associate Professor of Medicine and of Preventive Medicine and Public Health, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

JAMES F. HAMMARSTEN, M.D.—Chief, Medical Service, Veterans Administration Hospital, Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

WILLIAM O. SMITH, M.D.—Assistant Chief, Radioisotope Service, Veterans Administration Hospital, Assistant Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

LEONARD P. ELIEL, M.D.—Professor of Research Medicine, University of Oklahoma School of Medicine, Director of Research and Head of Cancer Section, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma

JOHN F. MUELLER, M.D.—Assistant Professor of Medicine, University of Cincinnati, Cincinnati, Ohio

The Renal Regulation of Acid-Base Balance: A Summary of Current Views

ARNOLD S. RELMAN
WILLIAM B. SCHWARTZ

CONTINUOUSLY, in the course of health and disease, the extracellular fluid is being assaulted by acids and bases of exogenous and endogenous origin. Despite this, even in the most extreme acid-base disturbances, blood pH rarely varies by more than 3 or 4 tenths of a pH unit. This fluid owes its remarkably stable hydrogen ion concentration in part to the buffering actions of the carbonic acid-bicarbonate system and the numerous other buffer systems in red cells, bone and soft tissues with which the extracellular fluid appears to be in equilibrium. The lungs also contribute their vital share to the acid-base defenses by providing a route for the regulated excretion of CO_2 from the blood. Excretion of acid (hydrogen) or alkali (bicarbonate or other titratable alkaline anions) is, however, a function reserved exclusively to the kidney. It is only because of this renal activity that the body buffers can be restored to their original equilibrium state after the initial impact of the acid or base load has been absorbed. Without renal function, buffering capacity would quickly be exhausted and the pH of the body fluids would be at the mercy of whatever excess acids or bases chanced to appear.

Renal regulation of acid-base balance is primarily a tubular activity since the glomerular function of the kidney appears to be simply an ultra-filtering step which is inherently incapable of changing the acidity of the plasma. Three operations of the tubule can be distinguished in this regard: A) Reabsorption of bicarbonate, B) Excretion of acid buffered as ammonium, monobasic phosphate and other stronger acids, and C) Excretion of free hydrogen ion in minute quantities, i.e., establishment of a urine to plasma hydrogen ion gradient. Very little is known about the molecular basis of these operations, hence it cannot be stated to what extent they represent distinct or interrelated mechanisms. The distinctions made here are purely for descriptive purposes, although, as will be made clear, they are not without a certain amount of experimental support.

A. *Excretion and Reabsorption of Bicarbonate.* The bicarbonate ion is freely filtered at the glomerulus and distributed across the glomerular membrane according to the Gibbs-Donnan equilibrium. Considering the relatively huge daily volume of glomerular filtrate (180 liters) this means that a quantity of bicarbonate many times larger than the amount in extracellular fluid is poured into the renal tubules each day. One of the important factors determining the concentration of bicarbonate in the extracellular fluid is therefore clearly the rate at which this ion or some product thereof is reabsorbed by the renal tubules.

Micropuncture studies in amphibia and mammals provide evidence that under normal circumstances bicarbonate is removed in proportion to water all along the proximal convoluted tubules. At the end of this portion of the nephron approximately 85% of the glomerular filtrate and its contained bicarbonate have disappeared, and the pH of the tubular fluid is still that of the plasma and the glomerular filtrate. However, virtually none of the filtered bicarbonate escapes reabsorption, because practically all that enters the distal tubule is removed by the time the final composition of the urine has been achieved. It is during this final reabosorptive process that the pH of the tubular fluid is reduced to that observed in the urine. Whether the reabsorption of *all* bicarbonate, including the most distal fraction, is accomplished by a single mechanism cannot be stated at present.

On the basis of a good deal of circumstantial evidence which cannot be detailed here, it is widely believed that most, if not all, bicarbonate is removed from the filtrate by tubular secretion of hydrogen ions and conversion of the filtered bicarbonate to carbonic acid. It is thought that this reaction is accomplished by an ion exchange process in which hydrogen ions from the tubular cell are exchanged for sodium ions in the glomerular filtrate. In the tubular fluid carbonic acid then disassociates into CO_2 and water, and the highly diffusible CO_2 rapidly moves back into the

plasma. In the process of secreting hydrogen ions the tubular cell simultaneously generates alkali which diffuses out of the cell into the plasma in the form of bicarbonate. Thus, the bicarbonate ion which appears in the renal venous plasma as the net result of the reabsorptive process is not actually the same ion which was removed from the filtrate, but the total effect is as if this ion were directly taken from the filtrate back into the blood. It seems likely that carbonic anhydrase activity inside tubular cells is necessary for reabsorption of bicarbonate since this process can be immediately slowed by the administration of a fairly specific enzyme inhibitor such as acetazolamide. The function of carbonic anhydrase is believed to be in catalyzing the reactions

$$1)\ CO_2 + H_2O \rightleftharpoons H_2CO_3$$

$$\text{and } 2)\ CO_2 + OH^- \rightleftharpoons HOC_3^-$$

Reaction 1 proceeding rapidly in the direction left to right might provide the source of intracellular hydrogen ions necessary for H-Na exchange. Alternatively, the hydrogen ions might come from other intracellular acid sources and the essential function of the enzyme might consist in facilitating the shift of Reaction 2 from left to right, allowing CO_2 to buffer the hydroxyl ions which would otherwise be accumulating in the tubular cells as they continued to secrete hydrogen ions.

For practical purposes, these two possible functions of carbonic anhydrase would be indistinguishable. In either scheme, a carbonic anhydrase-catalyzed reaction would be an essential step in the reabsorptive process and a critical reduction in enzyme activity would be expected to lower the renal threshold for bicarbonate. Carbonic anhydrase appears to be involved in the reabsorption of at least the great bulk of the filtered bicarbonate, since administration of acetazolamide under normal circumstances may divert more than half of the filtered load into the urine. Even when the plasma bicarbonate level is very low and the initial rate of reabsorption a small fraction of the normal, inhibition of carbonic anhydrase will appreciably diminish the rate of reabsorption.

Under normal circumstances virtually all of the filtered bicarbonate is reabsorbed when the plasma bicarbonate level is substantially below normal. As the plasma level is progressively raised by infusion of bicarbonate, increasingly large amounts of bicarbonate appear in the urine beginning at plasma levels around 24 or 25 mEq/L. Net reabsorption of bicarbonate, calculated as the difference between the filtered load (plasma level x glomerular filtration rate) and the rate of excretion, remains constant despite progressive elevation of plasma level. This abrupt saturation of the capacity of the tubule to reabsorb bicarbonate establishes a fairly sharp renal threshold for this ion and thereby determines the upper limit of the plasma bicarbonate concentration. Only by continuous and rapid administration or endogenous generation of alkali could the blood bicarbonate level be maintained above the renal threshold for any length of time.

Changes in renal threshold occur in a variety of clinical and physiological circumstances and are of the greatest importance in understanding acid-base adjustments in health and disease. A partial list of the factors which influence bicarbonate reabsorption include: 1) the CO_2 tension of the blood (pCO_2), 2) potassium balance, 3) sodium balance, and 4) drugs (e.g., acetazolamide) and 5) tubular diseases which may temporarily or permanently interfere with the integrity of the reabsorptive mechanism.

It has been found that the renal bicarbonate threshold tends to vary directly with the blood carbon dioxide tension. Precisely how this is accomplished is not known, but the physiological and clinical importance of this relationship is obvious. In respiratory acidosis the blood bicarbonate level tends to rise as an initial result of the buffering of carbonic acid by the hemoglobin or red blood cells and probably by buffers in other tissues as well. Later, increased renal excretion of ammonium and possibly also titratable acid serve further to raise the bicarbonate, as will be discussed in a subsequent section. The rise in blood bicarbon-

ate, tends to neutralize the acidifying effect of the increased pCO_2 and is essential to the maintenance of a normal blood pH. If the renal threshold for bicarbonate did not rise under these circumstances the extra bicarbonate in the blood would immediately spill out into the urine and effective compensation would be impossible. Actually, however, chronic elevation of blood CO_2 tension results in an appropriate rise in bicarbonate threshold which keeps the bicarbonate in the blood.

The reverse situation is seen in respiratory alkalosis. Sudden reductions in blood CO_2 tension resulting from increases in ventilatory volume result in a shift of bicarbonate ions into red cells and perhaps other tissues in exchange for chloride. The resultant drop in blood bicarbonate tends to minimize the rise in blood pH resulting from the reduced CO_2 tension, but were it not for a sudden increase in the renal excretion of bicarbonate, extreme rises in pH would nevertheless occur. Diuresis of bicarbonate in this situation is the result of a reduction in the tubular reabsorption attendant upon the change in pCO_2.

This physiological relation between respiratory function and bicarbonate reabsorption may not always serve the best interests of acid-base equilibrium. In chronic metabolic alkalosis the blood bicarbonate level is elevated due to excessive ingestion or endogenous production of alkali, or to excessive loss of acid from the body. Respiratory compensation for the rise in blood pH may sometimes result in appreciable reductions in ventilation and some rise in blood pCO_2. This, in turn, elevates the renal bicarbonate threshold and therefore maintains the abnormally high blood bicarbonate levels, even after the initiating cause of the alkalosis may have disappeared.

Changes in the tubular transport of either sodium or potassium may have important effects on the renal reabsorption of bicarbonate. Since the first step in the reabsorptive process appears to be an exchange of sodium in the filtrate for hydrogen in the tubular cells *(vide supra)* it would seem reasonable to expect that circumstances which stimulate sodium reabsorption would also tend to favor bicarbonate reabsorption and thus to increase the renal threshold for bicarbonate. Stimulation of sodium reabsorption by sodium depletion or by administration of adrenocortical salt retaining hormones has been found to have precisely this effect, although the action of the latter probably involves loss of potassium as well.

The relationship between potassium metabolism and bicarbonate excretion seems best explained at present by the hypothesis that potassium is excreted to a large extent, if not entirely, by tubular secretion, and that potassium and hydrogen ions compete for the same secretory pathway. Secretion of both ions is thought to involve the simultaneous reabsorption of sodium. According to this view, potassium-deficiency and a lowered concentration of potassium in tubular cells would favor exchange of hydrogen for sodium and would tend to increase the reabsorption of bicarbonate. Conversely, increased amounts of potassium in the blood and in the renal tubular cells forces increased secretion of this ion and competitively inhibits the simultaneous secretion of hydrogen. This would tend to reduce the rate of bicarbonate reabsorption and tend to alkalinize the urine.

Many clinical and experimental facts appear to fit this hypothesis. There is a high renal threshold for bicarbonate in states of potassium-deficiency, and this is largely responsible for the maintenance of the high blood bicarbonate levels which are such a frequent feature of potassium-depletion. (The kidney, however, is not usually the *cause* of this alkalosis, which apears in many cases to be due to a shift of extracellular hydrogen into cells as potassium is lost.) Despite the increased bicarbonate threshold in this situation, the urine pH tends to rise slightly as the potassium-deficiency develops, indicating a decrease rather than increase in the bicarbonate reabsorbed at some distal point in the tubule.

An elevated blood pCO_2 may also play a role in increasing bicarbonate reabsorption in states of potassium-deficiency, but it has been shown that the rise in threshold at any

given elevation of pCO_2 is greater in the presence of potassium-depletion. The converse relationship between potassium and bicarbonate can also be demonstrated. Rapid infusion of potassium in normal subjects will abruptly lower the threshold, increase bicarbonate excretion and produce metabolic acidosis. Even when the threshold is elevated by a high pCO_2, infusion of potassium will cause a bicarbonate diuresis.

Changes in carbonic anhydrase activity are also responsible for important effects on bicarbonate excretion. The acidosis produced by administration of acetazolamide is thought to be the direct result of inhibition of tubular carbonic anhydrase and the consequent reduction in bicarbonate reabsorption. Immediately following the administration of this drug there is a bicarbonate diuresis and the blood bicarbonate level falls. Continued administration of the drug results in stabilization of the blood bicarbonate at some moderately low level, but the urine bicarbonate excretion tends to return to pretreatment levels. This phenomenon also accounts for the self-limiting diuretic action of this compound, and its ineffectiveness in patients with metabolic acidosis. In acute experiments in dogs doses equivalent to those used clinically have little or no effect when they are administered at plasma bicarbonate levels below 12 to 15 mEq/L.

In renal disease acidosis results from tubular damage and impairment of some or all of the mechanisms for maintenance of acid-base balance. In some cases the renal threshold for bicarbonate has been found to be significantly reduced. It is possible that this is due to a reduction in carbonic anhydrase in the tubular cells, although other explanations can not presently be ruled out. In such patients elevations of blood bicarbonate to normal levels by infusion of bicarbonate results in rapid excretion of this ion until the plasma concentration has fallen to the level of the renal threshold. At this point bicarbonate excretion in the urine ceases to be significant and in some patients a further degree of acidosis may even stimulate the production of urines of pH 5.0-5.5. Patients with so-called renal tubular acidosis have more difficulty in acidifying their urine, the pH of which is usually found to b above 6.0 even with severe acidosis. Howeve when they are loaded with bicarbonate, th magnitude of their urinary bicarbonat "leak" is no greater than that of some pa tients with other forms of renal disease wh excrete more acid urines when they are acid otic.

B. *Excretion of Acid.* The two importan mechanisms by which the kidney gets rid o acid from the body are: 1) excretion o hydrogen buffered in the form of weak acids ("titratable acidity"), and 2) excretion o hydrogen buffered by ammonia in the form of ammonium ion. The net effect of either process on acid-base economy is the same, since a milliequivalent of hydrogen is lost from the body with each milliequivalent of ammonium or titratable acid. This means that the plasma returning from the kidney must have a higher concentration of bicarbonate than that in the renal artery because removal of hydrogen has the same chemical effect as addition of alkali.

Normally, the most important weak acid excreted in the urine is the monobasic phosphate ion ($H_2PO_4^-$, pK′ approximately 6.8). To a much smaller extent, hydrogen is also carried out in the form of relatively weak organic acids such as creatinine (pK′ approximately 4.97). Since the pH of the urine rarely gets much below 4.5, it is clear that the concentration of hydrogen ions excreted in the urine is always very low (less than 10^{-4} M/L) and almost no titratable hydrogen can be excreted in the form of acids with pK's below 3.0. The term "titratable acid" ordinarily refers to the urinary hydrogen which can be titrated between the pH of the urine and that of the blood. This virtually excludes all acids with very low pK's, e.g., the mineral acids and the stronger organic acids or very high pK's (e.g., NH_4^+).

Conversion of alkaline to acid phosphate ($HPO_4^{--} \rightarrow H_2PO_4^-$) is thought to be accomplished in the distal part of the convoluted system by the same kind of sodium-hydrogen exchange mechanism as that involved in the reabsorption of bicarbonate. It cannot be said for certain that this process, like that for bicarbonate, is dependent on carbonic

nhydrase activity, although this seems ikely. Administration of acetazolamide increases excretion of bicarbonate and therefore raises the pH of the distal tubular fluid. Even if the secretion of hydrogen for excretion as titratable acid were a process separate from bicarbonate reabsorption and were not directly inhibited, the net effect of alkalinization of the urine would be to reduce the excretion of phosphate in the acid form.

On ordinary diets under usual conditions normal subjects excrete about 20 or 30 milequivalents of titratable acid per day, but under certain circumstances this rate may be substantially reduced or may be increased by several fold. The maximal excretion of titratable acid is determined by the urine pH and by the total amount of buffer that can be excreted. Titratable acid may be greatly increased by infusion of phosphate into acidotic subjects, but unless there is a disturbance such as diabetic acidosis which leads to an increased excretion of one or more organic acids, there is ordinarily only a modest increase in titratable acid excretion in acidotic states. This results from the fact that in metabolic acidosis, for example following ammonium chloride administration, there is only a slight phosphate diuresis. Since the pK′ for monobasic phosphate in urine is approximately 6.8, it is clear that relatively little increase will be produced by reducing urine pH much below 6.0. In contrast, in diabetic acidosis where there is a large increase in the excretion of diacetate (pK′ approximately 3.8) and betahydroxy butyrate (pK′ approximately 4.7), titratable acid excretion may rise to more than 100-150 mEq/day. In this latter circumstance the pH of the urine is of great importance since the maximum buffering of these compounds in urine takes place below a pH of 5.5. Most patients with acidosis due to renal disease, except some with so-called renal tubular acidosis, are able when acidotic to elaborate urines of pH 6.0 or below, and hence they may excrete approximately normal amounts of titratable acid. However, if they have a low bicarbonate threshold, as noted above, their urines may be quite alkaline when attempts are made to raise their plasma bicarbonate toward normal, and under these circumstances they can excrete little or no titratable acid.

Usually, the greatest burden of urinary hydrogen is carried by the ammonium ion. In states of severe chronic acidosis healthy kidneys may excrete as much as 300-500 mEq/day. No direct information exists concerning the exact mode of excretion of ammonium. It is known that ammonia is synthesized in the renal tubules by enzymatic deamination of alpha-amino acids, chiefly glutamine. Glutaminase activity and the availability of amino acid substrate are therefore important factors in determing the production of ammonia. Because ammonia is a relatively strong base (pK′ approximately 9.3) and the maximum urinary pH is rarely above 8.0, almost all must be excreted in the acid form as the ammonium ion. All other things being equal, the urinary excretion of ammonium seems to be an inverse function of the urine pH, and this is also true of the excretion of certain other organic bases which are believed to be secreted by the tubules and have pK values similar to ammonia. For this reason, and also because cell membranes are usually more permeable to the free ammonia base than to the ammonium ion, it is now believed that it is the free base which diffuses into the tubular fluid. Hydrogen transferred to the tubular fluid in the process of sodium reabsorption is then buffered by combination with the base to form ammonium. The dependence of ammonium excretion on urine pH may be explained by the greater tendency of the free base to diffuse into an acid medium than an alkaline one. As the pH of the tubular fluid rises, the concentration of the free base also rises and hence the gradient for diffusion from the tubular cells into the fluid would fall.

The physiological factors regulating excretion of ammonium are not well understood. Ammonium excretion in various clinical and physiological states is clearly not simply a passive function of the urine pH. It is often found to vary independently of the latter. Furthermore, the correlation with blood pH is rather poor, although the acidity of renal tubular cells may be more directly concerned with ammonium excre-

tion. With continuous administration of acidifying salts to normal subjects, ammonium excretion rises progressively until it is virtually equal to the administered acid load. This rise occurs despite the fact that after an initial fall urine and blood pH remain fairly constant. It has been shown that prolonged acidosis causes some sort of enzymatic adaptation, with an increase in glutaminase activity and a greater capacity for tubular production of ammonia.

Another important factor which appears to influence ammonium excretion and which may play a role in the increasing response to continued loading with acid salts is the intensity of the stimulus to sodium reabsorption in excess of urinary anion. The ammonium response to a given load of ammonium chloride is greater in salt-depleted subjects, and salt-depletion becomes progressively more severe as the ammonium chloride is administered. Administration of DOCA causes an immediate increase in ammonium excretion, but only when there is a substantial amount of sodium in the diet. In neither situation can these changes in ammonium excretion be correlated with an increased acidity of urine or blood. A more reasonable explanation appears to reside in the sodium transport mechanism, since reabsorption of sodium without accompanying anion would tend to create a potential gradient which would favor the excretion of other cations, such as ammonium and potassium.

Potassium metabolism also influences ammonium excretion. When tubular cells are deficient in potassium as the result of serious body deficits of this ion, ammonium excretion tends to be somewhat higher than might be expected from the relatively high urine pH so characteristic of this condition. This effect may be due to a number of factors: a) renal glutaminase activity is increased in experimental potassium-depletion, b) the acidity of tubular cells may be increased, thereby favoring the H-Na exchange which is ultimately responsible for ammonium excretion, and c) less cellular potassium is available for secretion, thus increasing the electrostatic requirement for cation in the form of ammonium. The high ammonium excretion in primary aldosteronism is probably due in part to the severe coexisting deficiency of potassium. Furthermore, as might be predicted from the relationship of ammonium excretion to sodium reabsorption, excretion of ammonium in aldosteronism is increased when salt is added to the diet and reduced when salt is withdrawn.

In renal acidosis ammonium excretion is almost always reduced, even when urine pH is low. This is presumably due to structural or biochemical defects which sharply limit the capacity of the tubular cell to generate free ammonia or to a reduction of total tubular mass. In patients with constantly alkaline urines, such as those with so-called renal tubular acidosis, an unfavorable diffusion gradient for ammonia may also be a limiting factor. Whatever the explanation, the inadequate ammonia response in renal patients is clearly a major factor in the pathogenesis and maintenance of acidosis, usually of greater importance than any reduction in the capacity to excrete titratable acid. Without an ability to greatly increase the excretion of ammonium, patients with renal disease cannot effectively regenerate their body buffers and therefore are at the mercy of dietary or endogenous acids.

C. *Acidification of the Urine.* The glomerular filtrate is formed at the pH of the plasma, but bladder urine may be as alkaline as pH 8.0 or as acid at 4.0. Changes in pH are apparently accomplished in the distal convoluted tubules. Maximal acidification of the urine requires that almost all the bicarbonate remaining in the tubule be removed, and that any urinary buffers with pK's in the range of 3.5-5.0 be at least partly titrated with hydrogen. Although the pH of renal tubular cells is not known precisely, it may be estimated that at some distal point in the tubule hydrogen ion gradients across the cell membrane may approach 1000 to 1. It is assumed that this final operation involves the same sodium-hydrogen exchange process which is responsible for the reabsorption of bicarbonate, and the excretion of ammonium and titratable acid by the other parts of the distal tubule. However, there is some evidence to suggest that the acidifying function can vary independently of the

bicarbonate threshold and the capacity for ammonium excretion. In severe potassium-depletion, for example, there is a defect in acidification, but ammonium excretion and the threshold for bicarbonate are increased. In certain types of renal disease, furthermore, it has been observed that the capacity to acidify the urine may be relatively well preserved even when the bicarbonate threshold is lowered and ammonium excretion sharply curtailed.

Little is known about the physiological regulation of urine acidity. In dogs there is relatively little response to acute respiratory or metabolic acidosis even when very severe. In general, however, the urine pH does tend to vary with the acid-base balance of the body under many circumstances. There is some reason to believe that the acidification function and ammonium excretion bear the same relation to sodium reabsorption. It can be shown, for example, that rapid infusion of sodium sulfate will cause intense acidification of the urine if the subject has previously been stimulated to retain part of the infused sodium load by a low sodium diet and adrenal steroids. Under normal circumstances the same sulfate load is without effect on urine pH. It is possible to explain this phenomenon by postulating that acidification will occur whenever distal sodium reabsorption is rapidly increased in excess of anion and when the unreabsorbed anion remaining in the urine is of very low buffer capacity. An inportant stimulus for acidification may well prove to be sodium reabsorption rather than any direct or immediate consequence of acidosis.

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DISCUSSION

DOCTOR L. L. CONRAD, Assistant Professor of Medicine, University of Oklahoma School of Medicine, Chief, Cardiovascular Disease Section, Veterans Administration Hospital, Oklahoma City, Oklahoma: Doctor Relman, would you review those factors which are pertinent in the determination of intracellular pH? What are the determining factors, and how do you determine intracellular pH?

DOCTOR RELMAN: That is a very difficult question to answer. Most of our information about intracellular pH is indirect. The actual measurement of hydrogen ion concentration inside living cells is a formidable technical problem which has not been satisfactorily solved. We can measure the bicarbonate, or I should say we can measure the total CO_2 content of the tissues, and if one depletes tissues of potassium, the total CO_2 content goes down. If one keeps these tissues in a constant CO_2 tension, then making some

reasonable assumptions about the dissociation constant for carbonic acid inside tissues, one can say that pH has gone down; but the fact of the matter is, most of our information about intracellular pH is largely a matter of bookkeeping. You calculate with reasonable accuracy how much potassium has left the cell, you calculate with somewhat less accuracy how much sodium has gone into the cell, and then you say somewhat hesitantly with not very much confidence that maybe the discrepancy between the potassium out and the sodium in is accounted for by hydrogen ion. This is rather uncertain, and we have a lot to learn about intracellular pH.

DOCTOR CONRAD: I have a question for Doctor Heller or Doctor Relman. Is plasma bicarbonate content or plasma pH any index of tissue potassium deficit in metabolic alkalosis with hypokalemia?

DOCTOR HELLER: I would say that tissue potassium deficits may be associated with elevations of plasma bicarbonate content, and thus with increase in the pH, but all states in which there is an increase of the plasma bicarbonate content need not necessarily be associated with potassium deficit. In general, when hypokalemia and metabolic alkalosis co-exist, I think that the degree of metabolic alkalosis is roughly correlated with the degree of tissue potassium deficit. Potassium depletion, however, may be associated with a high pH, a low pH, or a normal pH.

DOCTOR RELMAN: I would like to add one comment. I think that the fairly quantitative relationship between extracellular bicarbonate and intracellular potassium holds true for very restricted and specific experimental situations, namely the type of potassium depletion produced, but in clinical practice one can see potassium deficiency occurring with acidosis or with alkalosis or with a normal pH. The type of acid-base disturbance and the severity of this disturbance in clinical practice, as far as I can see, has no predictable relationship whatsoever with intracellular potassium deficit. Thus, for example, in uremia you can have potassium depletion with acidosis; and in severe diarrhea, with loss of alkali in the stools, you can have potassium depletion with acidosis. With ammonium chloride poisoning, you can have acidosis and potassium depletion.

So, I would certainly agree with Doctor Heller and I would emphasize his point that it depends on how the potassium depletion is produced.

DOCTOR CONRAD: What is your experience with Diamox in respiratory acidosis with chronic pulmonary disease? Would you care to comment on that?

DOCTOR RELMAN: Doctor Leaf, Doctor Schwartz and I[1] a number of years ago treated a series of patients with respiratory acidosis and congestive failure with Diamox and observed some improvement with diuresis in about half of the group. We have not had any experience with pulmonary insufficiency or respiratory acidosis without congestive failure.

DOCTOR CONRAD: Patients with liver disease treated with Diamox may develop liver failure and elevated blood ammonia concentrations. Would you comment on that observation.

DOCTOR RELMAN: This is an interesting phenomena which has ben observed by a number of workers. Roberts and co-workers[2, 3] at Memorial Hospital, have pointed out that the symptoms of ammonium intoxication are probably due to intracellular concentrations of free ammonia base. If I recall their work correctly, they produced symptoms of ammonium intoxication by respiratory alkalosis in compensated patients with potassium insufficiency and improved the symptoms with respiratory acidosis. And, of course, these two conditions would change intracellular pH.

Now it seems to me, although this is all speculation, that a reasonable hypothesis for the action of Diamox would be that by inhibiting carbonic anhydrase in some critical cells, perhaps the brain or elsewhere, changes intracellular pH, and it is this that may produce ammonium intoxication.

DOCTOR CONRAD: Would you compare the action of chlorothiazide with that of Diamox on the kidney tubule.

DOCTOR RELMAN: Chlorothiazide is a sulfonamide and does have some carbonic anhydrase inhibiting activity. Compared to Acetazolamide, or Diamox, it is relatively weak, but it will alkalinize the urine slightly and increase the excretion of bicarbonate slightly. It does not owe its diuretic action, however, to this effect, in contrast to Diamox, which usually produces no increase of chloride and increases sodium excretion only by increasing bicarbonate. Chlorothiazide does have a large effect on the reabsorption of sodium chloride, so that one does observe with the administration of Chlorothiazide a slight increase in the excretion of bicarbonate but a much greater increase in the excretion of chloride and sodium. Whether chlorothiazide works on the reabsorption of chloride primarily or on reabsorption of sodium, and whether it affects the same mechanisms that are affected by mercurial diuretics is, so far as I am aware, as yet unknown.

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The Relations of Potassium Depletion to Renal Structure and Function

WILLIAM B. SCHWARTZ
ARNOLD S. RELMAN

POTASSIUM IS an essential, although not entirely irreplaceable, structural component of all cells. It appears, furthermore, to be an activator of certain enzymatic reactions involved in intermediary metabolism. In renal tubular cells, however, potassium plays still another role. There, it is an active participant in the ion exchange reactions through which renal regulation of electrolyte and acid-base balance is accomplished. It is not surprising, therefore, that severe chronic depletion of potassium should have profound consequences for both renal structure and function.

Rats placed on potassium-deficient diets within a few days begin to develop renal enlargement, which is followed shortly by the appearance of swelling, hyperplasia and granular changes in the epithelium of the collecting tubules. Obstruction leads to dilation of the convoluted system proximally, and low-power examination of the kidney usually discloses a striking cyst-like band of dilated tubules at the cortico-medullary junction. More advanced changes include various types of degenerative and necrotic lesions of the convoluted tubular epithelium, but for the most part there is relatively little damage to glomeruli, blood vessels, or other interstitial structures.

Restoration of potassium to the diet can produce complete healing of the renal lesions, but in some instances interstitial scarring and hyalinization of glomeruli have been noted long after correction of severe chronic potassium-deficiency. This may mean that the lesions of experimental potassium-depletion can become irreversible at some point, although this question has not been definitely settled.

The striking histologic effects of potassium-depletion in the kidney are accompanied by significant changes in the composition of renal tissue. Potassium content of the kidney is usually reduced by about 10-20%, although it is not proportionately as low as in muscle tissue and is not associated with a demonstrable increase in sodium. Lysine and arginine are increased, as in potassium-depleted muscle. Carbonic anhydrase and glutaminase activity are also increased. Histo-chemical techniques reveal increased acid phosphatase, TPN diaphorase and non-specific esterase activity in the tubular epithelium.

In man the renal lesion of potassium-deficiency resembles closely that of the rat in being confined chiefly to the tubular epithelium. Unlike the murine lesion, however, the human nephropathy is primarily a vacuolar and hydropic degeneration of the convoluted tubules, with the collecting tubules remaining unchanged in appearance. The vacuoles may be quite striking in their number, size and discreetness, sometimes appearing to occupy almost all of the tubular cytoplasm. They do not stain for fat, glycogen or protein, and usually seem to be relatively more numerous in the proximal than in the distal tubules. In many cases, however, these distinctive changes are not present or are relatively sparse. Less specific changes in the tubular epithelium may occur, including granularity, foamy swelling of cytoplasm and occasionally necrosis or sloughing of cells. Glomeruli, blood vessels and interstitial tissue are usually normal, unless there happens to be some other coexisting pathological process. Virtually no precise information is avalable concerning the minimum duration and severity of the potassium-deficiency required to produce significant lesions. By history, most of the cases observed to date appear to have been losing potassium for at least a month and usually much longer. In a few instances studied by serial biopsy well-developed lesions have been shown to be completely reversible when the potassium-depletion was repaired, but the question of possible irreversible or progressive renal disease in man has not been settled.

Lesions characteristic of potassium-deficiency have been observed in a great variety of clinical disorders. The most common cause is severe chronic diarrhea of any etiology, but hyperadrenalism (including Cushing's disease and primary aldosteronism) as well as renal tubular disorders with

urinary wasting of potassium have also frequently been at fault. The lesions due to potassium-deficiency are not infrequently found together with other independent renal pathology. It has been suggested that potassium-depletion makes the kidney more susceptible to pyelonephritis. While pyelonephritis has been often found associated with aldosteronism, the incidence in other types of potassium-depletion does not appear strikingly high. This question needs further study.

The most characteristic functional defect associated with potassium-depletion in both man and rat is an impairment of concentrating ability. In rats, and occasionally in man, this is accompanied by polydipsia and polyuria. Other tubular functions have not been systematically studied, but fragmentary observations in patients suggest that tubular transport of PAH and phenol red may sometimes be impaired. Despite the absence of significant glomerular lesions, filtration rate has been found moderately reduced in patients who become depleted from diarrhea, and there is a suggestion that this may be true for experimentally depleted rats as well. Blood nitrogen levels may be slightly increased under these circumstances. It is of interest, however, that a number of patients with potassium-depletion nephropathy resulting from aldosteronism have had entirely normal filtration rates. In many instances all the functional defects have proven to be largely or entirely reversible within a few weeks or months after correction of the potassium deficits.

Because active secretion of potassium appears to be closely linked to the other tubular exchange processes involved in the reabsorption of sodium and the secretion of hydrogen ions, it is not surprising that the renal tubular regulation of electrolyte and acid-base balance is significantly affected in states of severe potassium-deficiency. Presumably, this is the direct result of reduced potassium content of tubular cells, but since there is reason to believe that cells deficient in potassium also have an increased sodium content and acidity, it is possible that these latter changes also affect the ion exchanges in the tubule.

The important changes with severe chronic potassium-deficiency appear to be the following:

1. When potassium-depletion has been caused by extrarenal losses, there is a marked reduction in urinary excretion of potassium. This is presumably due to reduced distal tubular secretion of potassium, since most of the filtered potassium is thought to be reabsorbed in the proximal tubule. When the deficiency is due to hyperadrenalism (e.g., Cushing's syndrome or primary aldosteronism) or potassium-losing renal disease, the urine potassium content will naturally be high. Excretion of less than 10 milliequivalents of potassium per day ordinarily means that there is at least a moderately severe body deficiency and that this has come about through extrarenal losses.

2. There is an increased capacity for bicarbonate reabsorption, resulting in a high renal threshold for this ion. This change is responsible for the maintenance of the elevated plasma bicarbonate levels which are a common, although not invariable, feature of posassium depletion.

3. There is a tendency toward increased sodium reabsorption, which is responsible for the occasional development of edema. In primary aldosteronism there is usually no edema, possibly because the glomerular filtration rate tends to be relatively higher than in most other states of postassium-deficiency.

4. Ammonium excretion is somewhat increased, despite the fact that the urine is slightly more alkaline than usual.

5. The urine pH in severe potassium-deficiency rarely falls below 6.0 spontaneously, and tends to have a slightly higher than normal content of bicarbonate.

A reasonable, although entirely tentative, interpretation of these observations is as follows: Decreased cellular potassium content is directly responsible for the reduced secretion and excretion of potassium and is also accompanied by a significant increase in cellular acidity. The latter, in turn, fa-

vors the secretion of hydrogen in exchange for sodium in the tubular fluid, simultaneously resulting in increased reabsorption of bicarbonate and sodium and increased excretion of ammonium. Increase in renal glutaminase activity caused by the change in cell composition may also increase ammonium excretion. The tendency toward relatively alkaline urine may be attributed to a non-specific distal tubular defect comparable to that which impairs the urine concentrating mechanism, since it is presumably in the distal tubule that the normal urine to plasma hydrogen ion gradient is established. Alternatively, the relatively high ammonium excretion may result in a tendency for the plasma bicarbonate to rise above the renal threshold, even though the latter be increased by the tubular deficiency of potassium.

All of the above functional disorders associated with potassium-deficiency can be fairly rapidly reversed by restoration of the normal potassium balance. Thus, it has been observed that administration of potassium to depleted subjects results in: a) gradual increase in potassium excretion, b) a large diuresis of sodium, c) an abrupt reduction in the threshold for bicarbonate, d) a gradual fall in urinary ammonium excretion, and e) a slow return of urine pH to the usual range.

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DISCUSSION

DOCTOR ELIEL: Your discussion of potassium deficiency, centered about acute and subacute clinical states, can the same result appear after long-standing substandard dietary intake of potassium?

DOCTOR RELMAN: I don't know. I don't see any reason why chronic potassium depletion should not do everything that acute and subacute depletion does; and in fact, most of the patients that we have studied who were acutely depleted were fairly chronically depleted over a period of many months or perhaps years.

DOCTOR ELIEL: In potassium deficient states, is there evidence that protein utilization is impaired in spite of good protein intake? And is potassium necessary for adequate protein and carbohydrate metabolism?

DOCTOR RELMAN: There are no data in humans that I am aware of, but the work of Doctor Paul Cannon, of the University of Chicago, and others is quite definite on this point with regard to experimental animals. Potassium depleted animals do not use protein normally.

Furthermore, protein depletion will modify many of the effects of potassium depletion. In animals, in order to get many of the biochemical and physiological disorders that we associate with potassium depletion, one has to start out with a well-nourished animal and deplete him of potassium.

DOCTOR ELIEL: Now the next series of questions deals with the tissue changes subsequent to potassium depletion. I think that I might pose all of them and ask Doctor Relman to answer first and then Doctor Cooke.

The question is what evidence is there that potassium depletion leads to lesions in other tissues, particularly rapidly growing tissues such as gastrointestinal epithelium and bone marrow?

Are these changes in renal physiology which you have described the result of abnormalities secondary to hypokalemia? In other words, there are many secondary changes which result from decreased potassium. What changes are due to deficit of potassium ion itself?

Finally, have there been any studies on potassium depletion in children with celiac disease? Doctor Relman.

DOCTOR RELMAN: The first question about lesions in tissues other than the kidney, as you mentioned, Doctor Eliel, there are often lesions in the myocardium. We have not studied these lesions. They have been studied in detail by many other workers, but focal lesions have been reported and I believe that focal lesions, degenerative lesions in the skeletal musecles, have also been described.

We have been chiefly interested in the renal lesions. Grossly, there are striking changes in the gastrointestinal tract of experimental animals. Rats dying with potassium depletion have gross distention of their intestinal tracts. Sometimes this is full of fluid and this reminds one, of course, of the paralytic ileus and the distention that is often seen in patients who are clinically depleted of potassium.

With regard to the second question concerning the point about whether it is potassium itself or some secondary effect of the potassium which causes the renal lesion, I certainly cannot say. It seems to me impossible at this time to answer that kind of question because we simply do not know enough about

exactly what potassium does inside of the cytoplasm. All that we can say is that if you take potassium away, you produce the lesion; if you add the potassium, it goes away. What the sequence of events is, at the molecular level which explains these lesions, I simply do not know.

DOCTOR ELIEL: Doctor Cooke, can you answer the question about the celiac disease?

DOCTOR COOKE: I would like first to add a little to what Doctor Relman said. The stomach was shown by one of my students[1] a few years ago to have marked changes in its capacity to excrete acid during potassium deficiency. We did not see any anatomical changes and I don't know what the significance of that is.

The effect on the bone is one of the most interesting; not from a pathological standpoint, but from a functional standpoint. This is referrable to studies of Finberg[2] in Baltimore on patients with hypernatremia who, with gradual lowering of the sodium concentration, developel marked hypocalcemia.

In rats, as you remember, if one raises the sodium concentration and then lowers this with glucose and water, there is a very marked drop in calcium concentration of extracellular fluid. If you put potassium in during this period of time, for some reason, calcium remains in the extracellular phase and hypocalcemia does not occur; so that I think the bone gets into this problem of potassium depletion, but exactly how, we don't know.

And as regards the celiac disease, I am personally not too well acquainted with the problem of potassium deficiency in celiac disease. Actually, celiac disease is a disappearing disease; and over the period in which there has been a lot of interest in potassium metabolism, there has been less celiac disease than there used to be.

As far as the cystic fibrosis of the pancreas is concerned, there is a report in the New England Journal[3] that came from the Hospital of Medical Evangelists in California on potassium deficiency in cystic fibrosis of the pancreas. These authors attributed the potassium deficiency to the loss of potassium in the sweat.

We have studied this problem fairly extensively and the sweat potassium concentrations are a little higher in cystic fibrosis of the pancreas than in the normal. In our series, I think the concentration in the patients was 10 mEq/L and the controls were 6 mEq/L, which means that one would really have to sweat an awful lot more than any of these children do to get potassium deficient in this way.

I think it is more likely that when they are ill, they have a fair amount of vomiting and may well lose potassium in this way, and then become somewhat alkalotic and lose potassium in the urine as part of the mass sodium effect.

DOCTOR ELIEL: I have one question which is addressed to the problem of the relationship between tissue and serum potassium levels and clinical manifestations.

Doctor Darrow has indicated that it will take several days to replete the potassium depleted tissue and yet the clinical recovery from clinical manifestations of potassium deficiency occurs much more rapidly than that, in patients with diabetic acidosis and respiratory difficulties, for example.

What is the significance of the serum levels, the electrocardiograph changes, symptomatic manifestations and the actual tissue content of potassium? Doctor Relman, could you discuss this point for us?

DOCTOR RELMAN: That is a tough question. It has been our experience that in states of potassium deficiency with hypokalemia, the electrocardiogram is not a very accurate guide to the level of serum potassium and the degree of depletion. The serum level itself, on the other hand, is not a very accurate guide to the level of tissue depletion because many factors other than the total amount of potassium loss can change the serum level so that you cannot tell from the electrocardiogram, reliably, how depleted your patient is and you cannot tell from the serum level. Furthermore, the serum level and the electrocardiogram are only poorly correlated. This is in potassium-depleted states.

What about the other symptoms in potassium-depleted states; what explains the paralysis or the weakness; what exactly explains the renal lesion; is it the serum level or the tissue level? I don't think that one can draw any accurate relationship between any of these things.

Neuro-muscular function is affected by many different cations and many physical factors. We have to consider calcium, sodium, magnesium—many things that are not ordinarily measured simultaneously. We have to consider the rate of potassium depletion.

All these things play a role, and it is my experience that it is utterly impossible to know which patients are going to be paralyzed and which patients are not. I am constantly being surprised at the serum potassium levels. Patients will walk in, and clinically they don't look so bad—they have no reflex changes, their muscular strength is normal, and the serum potassium comes back 1.8 or 2.1 mEq/L.

Conversely, patients will come in with many of the symptoms which one would associate with potassium depletion, and the serum potassium may not be as low. So that I think one can make no hard and fast correlation.

On the side of hyperpotassemia, I think it is quite clearly shown by Doctor Tarail's studies and by the work of many people since, that the electrocardiogram in potassium intoxication responds to the serum level. It doesn't matter what the tissue level is—your patient will die of potassium intoxication when the serum potassium is 9 or 10 or 11 mEq/L., regardless of whether his tissues are overloaded with potassium or not. This is an acute thing which has to do with the extracellular concentration. I think one can forget about the tissues with acute potassium intoxication as far as the electrocardiogram is concerned.

When the electrocardiogram tells you that the patient has potassium intoxication, it is no sense to argue that the patient really has potassium depletion of his tissues and therefore he really needs more potassium. He will be just as dead of ventricular fibrillation, even though his tissues are depleted, as he would be if his tissues were normal.

DOCTOR ELIEL: Doctor Tarail, do you have any further comment about electrocardiograms and potassium?

DOCTOR TARAIL: I agree with Doctor Relman's splendid analysis of the various facets of the question, and I might just add a few things. Before you treat the patients with potassium, you must be sure that the patient's serum potassium is normal or low. Initially, in these patients, before rehydration, the serum potassium may be high in the face of a tremendous depletion of intracellular potassium; and, as Doctor Relman hinted, to fly in the face of a high serum potassium and administer potassium may result in a fatality.

In regard to paralysis, I think it is worth mentioning, to increase the puzzle, that it occurs also in patients with potassium intoxication.

Finally, electrocardiographic changes of potassium intoxication in man may occur at concentrations of serum potassium between 6 and 7 mEq/L.[4,5] This again emphasizes a more limited margin of safety than is implicit in a policy of cavalier administration of potassium to replenish supposed tissue deficit of the ion.

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Aldosterone and Potassium Metabolism

ROBERT E. COOKE

IN 1873 von Bunge[1] first described the inverse relationship of change in balance of sodium and potassium. The ingestion of potassium citrate or bicarbonate increased the excretion of sodium. Likewise an increase in sodium intake led to an increase in potassium excretion. The validity of these early experiments has ben confirmed many times.[2,3] Winkler and Smith[4] demonstrated that an intravenous load of potassium chloride led to an almost immediate rise in sodium and bicarbonate excretion. Leaf and Couter[5] showed that the intravenous administration of sodium salts, particularly sodium bicarbonate, was followed by a marked rise in potassium as well as sodium excretion. Obviously such a phenomenon under certain dietary conditions could lead only to depletion of the other cation unless some homeostatic mechanism was present to prevent such an occurrence.

It is the purpose of this paper to review the renal mechanisms responsible for the "Bunge phenomenon" and the mechanisms compensating for these changes through the secretion of aldosterone. Neither new nor original concepts are presented.

Sodium Excretion

Although alterations in glomerular filtration rate may lead to changes in sodium excretion, variations in tubular reabsorption are primarily responsible for fluctuations in the amount of sodium in the urine.[6] Sodium reabsorption is currently considered to result from exchange of cation of intracellular origin for intraluminal sodium.[7] Hydrogen ion which comes mainly from the dissociation of hydrated carbon dioxide is probably the principal cation exchanged throughout the proximal tubule. The quantity of sodium reabsorbed per unit time would seem to be limited by the supply of hydrogen ions from the renal tubular cells. In the more distal region of the tubule intracellular potassium may also be exchanged for the sodium reaching this site.

Potassium Excretion

Although the preliminary studies of Bott[8] indicated that filtered potassium was almost completely reabsorbed in the proximal tubule, more recent micropuncture studies by the same worker[9] demonstrate that a small but significant quantity of filtered potassium escapes reabsorption in the proximal tubule. If non-selective reabsorption of sodium and potassium occurs in the proximal tubule, 5 to 15 per cent of filtered potassium may reach the distal tubule. In addition potassium is exchanged for filtered sodium in the distal tubule. The latter process probably accounts for the major portion of excreted potassium. Increase in potassium excretion may be observed both when sodium excretion increases and decreases. Such a paradox is best explained by assuming that two factors are operative in potassium exchange: (1) the number (and possibly the concentration) of sodium ions reaching the exchange site—"the mass factor;" (2) the degree of substitution of potassium for a given number of sodium ions—"the percentage factor." If sodium diuresis occurs, potassium output increases (unless potassium exchange is blocked as in mercurical diuresis), since statistically the opportunity for contact with exchange sites is greatly increased. If exchange sites are more accessible to sodium ions and the supply of intracellular potassium to these sites is abundant, exchange of potassium increases and effects a decrease in sodium excretion. Limitation of sodium intake markedly restricts potassium loss even when large doses of desoxycorticosterone are administered to rats.[10] Administration of desoxycorticosterone to rats on a fixed sodium intake increases potassium excretion and decreases sodium excretion.

Interrelationships of Sodium and Potassium Excretion

When the potassium concentration of the plasma reaching the renal tubule is increased intracellular pH probably rises,[11] thereby reducing the availability of hydrogen ions for exchange with sodium. Sodium reabsorption decreases and sodium excretion increases. The increase in potassium excretion under these circumstances has been interpreted as resulting from a shift in the equilibrium in which potassium and hydrogen compete for exchange at the same level of the tubule.[7] Telelogically it would seem more reasonable to assume that the greater mass of sodium reaching the distal tubule after potassium loading increases absolutely the exchange of cell potassium for intraluminal sodium. Since potassium excretion is almost totally dependent on exchange for sodium such a mechanism would guarantee an increased capacity for renal excretion of potassium when the plasma potassium level rose.

An administered load of sodium increases potassium excretion acutely in the same way. Whenever the accompanying anion is reabsorbed to only a limited extent (such as phosphate, sulfate or bicarbonate) the quantity of sodium reaching the distal tubule is increased and potassium excretion also rises. Diuretics such is Diamox® or Chlorothiazide® probably increase potassium excretion in this way. However, kaliuresis is limited after the administration of mercurical diuretics because exchange of potassium is blocked by these compounds.

Compensatory Mechanisms

It is obvious that some homeostatic mechanism is necessary to prevent depletion of body sodium when potassium is given or potassium when sodium is given. That aldosterone represents such a feedback system can be concluded from a review of the action of this hormone and of the control of its secretion.

Action of Aldosterone

The effects of aldosterone on various organs are listed in Table 1. The predominant action is on the kidney tubule. Injection of 40 micrograms intravenously into a patient with Addison's disease leads to a rapid (less than one hour) decrease in sodium excretion.[12] The excretion of potassium increases and therefore a marked fall in the sodium to potassium ratio of urine occurs.[13] Urinary titratable acidity and ammonia excretion also increase. The increase in ammonium ions in the urine probably results from trapping of ammonia by hydrogen ions as the

PROBABLE ACTION OF ALDOSTERONE

Kidney
Increase Exchange
H for Na
K for Na

Gastrointestinal
Increase Exchange
Stomach: H for Na
Colon: K for Na

Sweat and Salivary Gland
Decrease Na in precursor fluid
or
Increase Na reabsorption in duct

Muscle
Increase Exchange
H_i and K_i for Na_e

Leukocyte
Increase Exchange
K_i for Na_e

Table 1

exchange of hydrogen for sodium is increased. Ammonia production by the tubules is probably not increased since renal glutaminase activity remains normal after adrenalectomy even though ammonium excretion falls.[14] Exchange of sodium for hydrogen or potassium in other tissues is probably affected by aldosterone. Output of hydrogen ion by the stomach[15] and exchange of potassium for intraluminal sodium in the intestine[16] are increased by aldosterone. Furthermore aldosterone reduces the sodium concentration of sweat and saliva and decreases the sodium to potassium ratio in these secretions.[17] It is also likely that the distribution of sodium and potassium within the body may be altered since adrenal steroids including desoxycorticosterone increase the sodium content of leukocytes in vitro and decrease intracellular potassium concentration.[18]

The fundamental mechanism by which aldosterone affects transport or exchange is unknown. It is possible that hormones possess a somewhat similar mechanism of action, analogous to the action of all vitamins as coenzymes. Insulin is thought to affect membrane permeability to glucose;[19] pitressin membrane permeability to water.[20] The observed action of aldosterone could be explained by assuming that the hormone affected membrane permeability to sodium. In the kidney tubule aldosterone might thereby permit greater penetration if intraluminal sodium into cellular exchange sites for hydrogen and potassium.

The Control of Aldosterone Secretion

Aldosterone output is affected by a number of factors and at present no single regulating mechanism can be identified. The study of this problem is complicated by the fact that only a small fraction of the total amount secreted can be recovered in the urine. Studies in which aldosterone is injected indicate that only 0.1 per cent of the administered dose is recoverable in the urine when extracted at pH 3.[21] When pH is lowered to 1 hydrolysis of certain excretory products occurs and the total recovered rises to 3 to 5 per cent. The study of secretory rate is also complicated by the fact that variations in inactivation by the liver occur.[22] Measurement of aldosterone levels in the peripheral blood is not feasible at present. Catheterization of the adrenal vein permits a direct estimate of production. However, small errors in measurement of blood flow alter considerably the calculation of daily secretory rate.

Although aldosterone output continues after hypophysectomy, ACTH increases somewhat the secretion of this hormone. Perfusion of the isolated beef adrenal with fluid containing ACTH leads to a rise in salt retaining activity of the venous effluent.[23] Administration of ACTH to the intact dog also increases the aldosterone level of adrenal vein blood. In the human a significant and moderately sustained increase in alderstone output occurs after ACTH administration when sodium intake is limited.[12] When ACTH is administered to a patient on a high sodium intake, there is a brief increase in urinary aldosterone, a decrease in urinary sodium, an increase in potassium excretion and an increase in body weight followed by a return of urinary aldosterone to control levels.

On the basis of transection experiments a neurohumoral mediator from the hypothalamus has been postulated.[24] However, these experiments are difficult to interpret

because of complicating factors such as blood loss, shock, anoxia, transfusions, etc., that may affect the adrenal directly.

Elevation of the serum potassium concentration leads to an increase in the aldosterone secretion. Perfusion of the isolated beef adrenal with a solution containing 25 mEq. per liter of potassium led to a significant increase in aldosterone concentration in the adrenal venous effluent.[23] In the intact animal that is sodium depleted potassium loading leads to a rapid rise in serum potassium concentration which in turn evokes an increase in aldosterone secretion.[25] When the intake of sodium is adequate, potassium loading produces neither a rise in potassium concentration nor an increase in aldosterone. In a patient with heart failure, edema and hyperpotassemia reduction of the serum potassium by means of Mercuhydrin® and a low potassium diet led to a fall in aldosterone excretion from 300 micrograms per day to 35. Water loading during pitressin administration increases total body water and lowers plasma sodium and potassium concentrations. Increase in dietary potassium chloride raises plasma potassium and aldosterone output.

The volume of body fluids may have even greater effect on aldosterone secretion than the concentration of potassium in plasma. The restriction of sodium intake with loss in body weight and body water leads to an increase in aldosterone secretion. Restoration of sodium to sodium-depleted subjects is followed by increases in body weight and body water and decreases in aldosterone output. This effect is not dependent upon changes in total body water but rather to changes in the extracellular space. Administration of hypertonic saline decreases aldosterone output even though intracellular water and total body water decrease. The blood volume affects aldosterone output rather than interstitial volume. Removal of blood with replacement by isotonic saline causes an increase in aldosterone secretion even though body weight and interstitial volume increase.[12] Removal of blood with reinfusion of cells in salt poor albumin causes a decrease in aldosterone output even though body sodium is diminished.

The Balance Between Immediate and Delayed Response to Electrolyte Loads

Such concepts of aldosterone action and control provide an explanation for the maintenance of relatively constant body composition despite wide fluctuation in electrolyte intake. When a load of sodium is administered, potassium excretion increases immediately. The excreted potassium comes from renal tubular cells[26] which in turn remove potassium from the plasma. The fall in plasma potassium concentration as well as the rise in effective circulating volume caused by the intake of sodium decreases adrenal cortical secretion of aldosterone. If renal tubular permeability to sodium is decreased by a fall in aldosterone levels, exchange of hydrogen and potassium for sodium decreases and sodium excretion rises as potassium excretion falls. Likewise reduced exchange of plasma potassium for sodium in the gastrointestinal tract tends to restore body composition toward normal.

On the other hand depletion of sodium by extrarenal routes such as in diarrhea leads to marked reduction in the quantity of sodium reaching exchange sites for potassium in the distal tubules particularly if glomerular filtration rate is lowered by concomitant circulatory insufficiency. The fall in extracellular volume and probably rise in potassium concentration under these circumstances effects an increase in aldosterone secretion. The elevated levels of aldosterone not only permit conservation of sodium but also facilitate potassium excretion. Increased gastrointestinal conservation of sodium and excretion of potassium also occur.

When a load of potassium is administered, sodium loss occurs immediately and depletion of sodium would result except for a rise in aldosterone output. The increase in plasma potassium concentration that results from such a load as well as the reduction in extracellular volume from sodium loss increases aldosterone secretion. Elevated levels of aldosterone increase sodium conservation and facilitate the excretion of potassium by increasing exchange in the distal tubule. The action of aldosterone on the gastrointestinal tract limits potassium absorption and conserves body sodium.

Depletion of potassium likewise reduces aldosterone output, potassium exchange in the renal tubule and potassium loss into the gastrointestinal tract thereby tending to restore body composition toward normal.

Conclusion

The immediate effect of loads of sodium or potassium is an increase in the urinary excretion of the other ion. Depletion of the ion the supply of which is limited is prevented by alterations in the output of aldosterone.

The mechanisms controlling the excretion of sodium and potassium and the secretion of aldosterone are discussed.

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DISCUSSION

DOCTOR ELIEL: Why do patients with primary aldosteronism fail to exhibit edema?

DOCTOR COOKE: I have no notion why. I would think that usually primary aldosteronism is associated with hypertension. I wonder whether or not there could be increased filtration rate and some loss of sodium in this way. I think this might be a possible explanation.

DOCTOR ELIEL: Doctor Relman, do you have anything to add?

DOCTOR RELMAN: I don't know the answer either, but I think the analogy between primary aldosteronism and normal patients given prolonged high doses of salt-retaining steroids is pretty good.

Now, if you take a normal man and give him Desoxycorticosterone or some other sodium-retaining steroid in high doses for a long period of time, you cannot produce edema. You produce first a phase of sodium retention which rapidly passes despite continued administration of the steroid, and the subject rapidly comes back into normal sodium balance.

This, I think, is the situation that we see in patients with primary aldosteronism. At the same time, there is a tendency for the glomerular filtration rate to rise in normal subjects given steroids, and this may be part of the mechanism which enables them to escape from the sodium-retaining action of the steroid. That there is such a mechanism, I think, is quite clear.

If you consider secondary aldosteronism, for example, someone who has edema from low plasma protein, from say the nephrotic syndrome or someone who has edema from congestive heart failure and an increased aldosterone output, you have a situation in which retention of sodium does not enable the renal circulation or the glomerular filtration rate to get the full effect of that retention because of the fact that

the sodium is being sequestered in the tissues. As far as the essential circulation is concerned, that sodium is not being retained—it is being lost into the tissues as a result of the high capillary pressure or the low colloid osmotic pressure. The idea that I am suggesting is simply that in primary aldosteronism, compensatory mechanisms, which may include increased glomerular filtration rate, come into play because the sodium remains in the circulation. In secondary aldosteronism, compensatory mechanisms do not come into play because that sodium is leaking out of the circulation into the tissues.

DOCTOR COOKE: Actually, I think one does see edema from salt-retaining hormones, but you have to look at a different species from the one Doctor Relman works in—namely, small babies. You will see edema develop under those circumstances very readily and each stress by itself actually will precipitate edema during their salt-retaining phase.

DOCTOR TARAIL: Perhaps I will have the courage to suggest an alternative possible explanation, although I suppose I will be stoned or throttled by my colleagues here. Perhaps this fact that patients with primary aldosteronism do not develop edema in the face of a tendency toward sodium retention is evidence against the idea that sodium has a great deal to do with it. Perhaps this is evidence against the idea that sodium retention is importantly involved in edema.

Acute Renal Insufficiency

BEN I. HELLER

NUMEROUS clinical disorders associated with transient hypovolemic shock, dehydration, depletion of sodium and chloride, metabolic acidosis, and trauma may precipitate varying degrees of decreased renal function and result in oliguria. If these disorders are promptly recognized and correctly treated, renal blood flow may be quickly restored to normal and anatomic alterations of the renal tubules will not occur. On the other hand, these same disorders of a more severe and persistent degree may cause an intense and persistent decrease in renal blood flow and acute renal insufficiency may ensue. During the past fifteen years a syndrome of acute renal insufficiency associated with a wide variety of precipitating factors has become recognized with increasing frequency. It is of the utmost importance that the syndrome be recognized early and proper treatment instituted promptly since errors in diagnosis and treatment may lead to the death of the patient.

Acute renal insufficiency may be defined as a syndrome of rapid but *reversible* loss of renal function due to renal ischemia or nephrotoxic agents and resulting in necrosis of cells of the proximal tubules and disseminated areas or tubular necrosis with disruption of the basement membrane in both the proximal and distal nephron.[1] Synomyms that have been used are acute renal failure, acute tubular necrosis, shock kidney, crush syndrome, hepatorenal syndrome, toxic nephrosis, hemoglobinuric nephrosis, burn nephritis, acute parenchymatous degeneration, extra-renal uremia, and lower nephron nephrosis. The term "lower nephron nephrosis," which implies localization of pathologic change to the distal nephron, is a poor one despite its wide acceptance, since the renal lesion is disseminated. The terms "acute renal insufficiency," "acute tubular necrosis," and acute renal failure appear to be gaining wider acceptance in current literature.

Pathologic Physiology

The majority of patients with acute renal insufficiency will have experienced shock due to blood loss, dehydration, or bacteremia. In those patients who do not manifest the clinical signs of peripheral vascular collapse, hemoconcentration and a deficit in circulating blood volume will frequently be present. The studies of Lawson and associates[2] indicate that the kidney participates to a pronounced degree in the vasoconstrictive phenomena of shock. The decrease in renal blood flow is considerably greater than the reduction in cardiac output, and the glomerular filtration rate and tubular function are greatly reduced.[3] Anatomic alterations of the renal tubules consisting of disseminated areas of tubular necrosis and disruption of the tubular basement membrane result from the renal ischemia and hypoxia.

Hemolytic transfusion reactions and other disorders associated with a hemolytic process are commonly followed by acute

renal insufficiency. The distal tubular lumina and collecting ducts are often obstructed by hemoglobin casts, but obstruction per se is not an adequate explanation for the oliguria. In some instances hemolytic transfusion reactions are associated with peripheral vascular collapse. Even when this is not present, however, the precipitation of the casts appear to be secondary to intense renal vasoconstriction, marked reduction of the glomerular filtration rate, and oliguria. In the crush syndrome, in which large amounts of myohemoglobin are released from striated muscle, renal insufficiency is produced through a similar mechanism.

Renal tubular necrosis is caused by numerous substances. Chief among these are carbon tetrachloride, mercuric bichloride, and the sulfonamides. The reduction in renal blood flow has been demonstrated to be secondary to the tubular damage produced by the nephrotoxic agent. The pathologic lesion produced by such agents is chiefly a necrosis of the proximal nephron cells without disruption of the basement membrane.[1]

The marked reduction in glomerular filtration rate associated with the intense renal ischemia is undoubtedly a factor in producing oliguria. Back-diffusion into the renal interstitial tissue of that glomerular filtrate which is being formed is probably the most important factor. Experimental evidence for the unselective back-diffusion of the glomerular filtrate across the damaged tubular membrane was first noted by Richards.[4] When phenol red was injected into the ureter of a frog's kidney immersed in oxygenated Ringer's solution, the phenol red remained concentrated in the loop of Henle. When hydrocyanic acid was injected into the kidney, the dye no longer remained concentrated in the tubules but diffused out into the surrounding renal tissue. Richards also noted that selective tubular function was abolished in the frog kidney which was poisoned by mercuric bichloride. He found that the glomerular filtrate appeared to be increased but no urine was formed. He concluded that the damaged tubular epithelium allowed the filtrate to be drawn back into the blood stream by osmotic pressure. The demonstration of disruption of the tubular cell basement membrane, the decreased $\frac{U}{P}$ ratios for creatinine and inulin and negative $T_{m\ PAH}$ values are all in keeping with this concept.

Clinical Course

The clinical course of acute renal insufficiency is extremely variable—the degree of variability depending upon the nature of the initial illness or injury, the degree of renal insufficiency and the rate with which it develops, the type of therapy, and the rate of recovery in renal function. In spite of the great variability in the clinical course, the syndrome may be divided into the following three phases: 1) shock, 2) acute renal insufficiency or period of oliguria, 3) the period of recovery in the early and late phases of diuresis.

The duration of the first phase will depend upon the promptness and adequacy of the treatment of shock. If dehydration is present, as it may be in patients during surgical operations, the volume of blood loss which may precipitate peripheral vascular collapse may be less than that causing shock in normally hydrated patients. Other symptoms and signs will, of course, depend upon the primary disease and associated conditions. Examples of such disorders are traumatic or operative shock from blood loss, post-partum or post-abortional bleeding, diabetic acidosis, and severe diarrhea. It must be empasized that shock may be absent according to the usual clinical criteria, but water and electrolyte losses may result in appreciable decreases in plasma volume and marked reduction in renal blood flow.

Following shock, hemolytic transfusion reactions, or the ingestion or inhalation of nephrotoxic substances there is a rapid development of progressive renal insufficiency. This is frequently ushered in by fever, nausea and vomiting, abdominal distention, occasionally jaundice, and pain in the costovertebral angle. Diminution in urinary output to 50-400 ml. per day is the general rule. The syndrome may develop in

spite of a daily urine volume of 400-1000 ml. per day. This was found in two of the 25 consecutive cases in our series (Table I).

DURATION OF OLIGURIA—25 CASES

Diagnosis	No. of cases	Days of oliguria	Deaths
CCl_4 Poisoning	12	3-15	2
Hypovolemic shock	6	6-15	4
Hemolytic transfusion reaction	3	1-7	1
Acute pancreatitis	2	6-11	1
Staphylococcal bacteremia	1	0	
Unknown (severe alcoholism)	1	9	1

TABLE I

The urine may be grossly bloody or smoky for the first few days; it is acid in reaction and contains large amounts of protein. The initial urine may have a high specific gravity but concentrating ability is rapidly lost, and the specific gravity becomes fixed at 1.010 to 1.012. The urinary sediment initially contains red blood cells, white blood cells, pigment casts, and hyaline and granular casts. The erythrocytes soon disappear from the urine, the proteinuria diminishes, and varying numbers of leukocytes may be seen.

As the oliguria persists, there is a marked tendency for the development of signs of congestive heart failure with pulmonary edema. This is especially true if salt and water are administered injudiciously. Cardiac dilatation, cardiac overactivity with loud heart sounds, gallop rhythm, elevated venous pressure, and normal or rapid circulation times are noted. The cardiac failure is of the high output type.[5] It is questionable whether a metabolic defect in uremia is responsible for the heart failure. In some instances the signs of congestive heart failure will resolve in the early phase of diuresis although there is a progression in the uremic syndrome. It is customary to administer digitalis to these patients, and we have followed this custom; but the efficacy of digitalis is questionable. There have been no definitive studies relative to the effects of digitalis either in this syndrome or in the high output failure of acute glomerulonephritis. When congestive heart failure develops, an analysis of fluid therapy and daily weights will usually reveal unmistakable evidence of overhydration. In an occasional patient, however, pulmonary edema will develop in spite of judicious therapy. It is conceivable that increased capillary permeability may play a role in this phenomenon.

Hypertension usually develops in the first few days, the systolic hypertension being more pronounced than the diastolic in most cases. In two of our patients there was a wide fluctuation in blood pressure from slight elevation to levels as high as 256 mm. mercury systolic and 140 diastolic. Eight of our 25 patients had normal blood pressure.

Gastrointestinal symptoms may continue in the oliguric period with abdominal distention, nausea and vomiting, and diarrhea. These symptoms, as is true of all others, may vary greatly from patient to patient. Two of the patients in this series had massive gastrointestinal bleeding. One patient had carbon tetrachloride poisoning in which the bleeding diathesis is generally more pronounced. One patient with hypovolemic shock sustained an episode of massive hematemesis on the sixth day of diuresis. Although this was promptly treated with blood transfusion and the period of shock was transient, oliguria recurred and death followed five days later from uremia and hyperpotassemia.

Cerebral symptoms are common and are similar to those seen in any patients with uremia. Restlessness, apprehension, delerium, and coma may be present. We have been impressed with the extreme apprehension, restlessness, and the expression of fear in patients with hyperkalemia. When convulsions occur, they will usually have been preceded by the administration of excessive amounts of salt and water.

Early deaths are usually due to the primary disease, but fatal pulmonary edema may occur early if incorrect therapy is given. Deaths later in the oliguric phase are

due principally to pulmonary edema, uremia, and hyperpotassemia (Table II).

CAUSES OF DEATH

Days of Oliguria	Day of Death	Cause
11	11	Pulmonary edema
8	8	Pulmonary edema
9	9	Pulmonary edema
3	7	Uremia
6	15	Uremia
15	15	Uremia, pulmonary edema
10	10	Hyperpotassemia
7	10	Hyperpotassemia
8	8	Uremia

TABLE II

Laboratory studies reveal a rapidly developing normocytic, normochronic anemia. The hemoglobin falls to 8 to 11 gms. per 100 ml. of blood within the first 10 to 14 days after the inception of oliguria. It then stabilizes at this level even though the oliguria may continue. The anemia is due to both decreased erythropoiesis and hemolysis. The anemia may persist for many weeks or months after recovery. In one patient the hemoglobin was 8.4 gms. per 100 ml. of blood during the phase of acute renal insufficiency. Five months later, at a time when renal function had returned to normal, the hemoglobin was 9.9 grams, and the anemia was unresponsive to iron. Since the anemia is well tolerated and since blood transfusion in the oliguric period may precipitate pulmonary edema, it is believed that blood transfusion is contraindicated.

Rapidly rising blood urea, decreased serum sodium, chloride, calcium and bicarbonate; and varying elevations of serum inorganic phosphorus and potassium are noted. Lowering of the serum sodium can frequently be accounted for by the dilution of body fluids by the parenteral administration of sodium-free fluids. In some patients, however, hyponatremia appears to be caused by intracellular shifts of sodium or extracellular shifts of water.

Potassium commonly rises to levels that are neurotoxic and cardiotoxic. The effets of hyperpotassemia are accentuated by coexistent hyponatremia, hypocalcemia, and metabolic acidosis, paresthesias of the extremities, muscular weakness, pain, and tenderness; flaccid peripheral paralysis and respiratory paralysis may occur when the serum potassium is above 8 mEq. per liter We have been impressed with the marked degree of apprehension, restlessness, and cloudiness of the sensorium which occur. Serial determinations of serum sodium and potassium and serial electrocardiogram are essential in following progress. The first electrocardiographic abnormality is the presence of high, peaked T waves with a narrow base, noted initially in the precordial leads and then in the limb leads. These are usually seen first in precordial lead V_2. This finding may quickly be followed by depression of the ST segment, varying degrees of auriculoventricular and intraventricular block, disappearance of the P wave, bradycardia, periods of asystole, and varying types of ventricular arrhythmias. It has recently been shown that elevation of the serum magnesium, even when the serum potassium is only slightly elevated, may give rise to the same signs and symptoms.[6]

Diuretic Phase

The average duration of the period of oliguria is 10 to 12 days but it may persist for as long as 21 days. The duration of oliguria in our patients varied from 3 to 15 days. As tubular regeneration occurs, there is a gradual increase in urine volume. Rapid and marked weight loss is noted with the onset of diuresis even in those patients who are not clinically overhydrated during the oliguric phase. The data of Swann and Merrill[7] indicate that the diuresis is related in part to retention of water during the phase of oliguria. This represents water of oxidation and the release of bound tissue water. The oxidation of one gram of carbohydrate, protein and fat will yield 0.55 ml., 0.41 ml., and 1.07 ml. of water respectively. The average daily fat consumption for two patients reported by Swann and Merrill was 310 grams and 255 grams. The average daily protein consumption was 48 grams and 22 grams. It is the contention of these authors that the quantitative replacement of fluid

and electrolyte losses during the diuretic phase results in a continuous, forced diuresis. There are, however, some patients in whom diuresis will be so intense that depletion of extracellular fluid and diminished blood volume will lead to circulatory collapse is adequate fluid and electrolyte replacement is not instituted. This occurred in two patients in this series.

The blood urea may continue to rise for several days after diuresis occurs. This is usually not cause for alarm, and steady improvement in the clinical course follows correct therapy. In other instances, however, symptoms and signs of acute renal failure will progress in spite of diuresis. The uremic syndrome may become intensified, and hyperpotassemia may progress. Twenty to 25% of the deaths reported in the literature occur during the diuretic phase. Of the 9 deaths among our 25 patients, three occurred during this phase.

Data relative to the urinary concentration of sodium and potassium is available for 10 patients. The mean urinary sodium concentration was 38 mEq. per liter with a range of 17-72 mEq/liter. The mean urinary potassium concentration was 27 mEq. per liter with a range of 20-31 mEq. per liter.

After clinical recovery normal renal function may not be reestablished for several months.[8] The ability to excrete a concentrated urine is the last function to return to normal.

Differential Diagnosis

The following diseases must be considered in differential diagnosis: Acute glomerulonephritis, acute exacerbation of chronic glomerulonephritis, acute pyelonephritis, ureteral obstruction from stone, sulfonamide crystalluria, metastatic cancer with ureteral obstruction, and renal vascular lesions such as malignant hypertension and renal infarction. The differential diagnosis of these diseases is usually not a difficult problem. As a general rule, in the absence of a history of a disease or an event known to precipitate acute renal insufficiency, the diagnosis will usually prove to be another form of renal disease. Anuria is rare in acute renal insufficiency. It is more commonly found in acute glomerulonephritis and in complete obstruction of the ureters.

Given a disease or a condition known to precipitate acute renal insufficiency, the urine volume should be carefully evaluated following blood replacement or electrolyte and water repletion. If oliguria persists following these therapeutic measures, a diagnosis of acute renal insufficiency may then be made.

Treatment During the Phase of Oliguria

The keynote of therapy during the oliguric phase of acute renal insufficiency is the rigid restriction of fluid intake. It has been estimated that the average insensible water loss from the skin and lungs of an afebrile adult patient is approximately one liter. Endogenous water formation from tissue catabolism and the release of bound water has been estimated to be approximately 450 milliliters per day. Since these figures are only approximations, the only reliable guide to proper fluid therapy is the daily body weight. In view of the fact that basic caloric requirements can usually not be provided to the oliguric patient, proper fluid balance should be accompanied by a small daily weight loss. This usually amounts to between one-tenth and four-tenths of a kilogram daily. Weight loss greater than .5 kilograms probably indicates dehydration. Maintenance of body weight or an actual gain in weight indicates overhydration. In our experience the usual daily fluid requirement has varied from 400 to 550 milliliters per day. This has been administered in the form of 50% glucose given via a polyvinyl catheter which has been threaded into the basilic or femoral vein. The degree of inhibition of tissue catabolism from the parenteral administration of glucose is variable. When acute renal insufficiency follows severe trauma or postoperative shock, the degree of inhibition does not appear to be very marked. On the other hand we have noted in patients with carbon tetrachloride poisoning that considerable protein sparing is achieved by this amount of parenteral glucose.

Oral alimentation should never be attempted early during the oliguric phace. Indeed, in our own experience alimentation attempted by oral routes even during the latter phase of oliguria frequently meets with failure. Various types of fat emulsions have been used with varying degrees of success. When fat emulsions are given orally even during the latter phase of oliguria nausea and vomiting and diarrhea are common occurrences. In only one patient in this series was a fat emulsion used successfully throughout the phase of oliguria. The administration of protein or potassium in any form is, of course, absolutely contraindicated during the oliguric phase.

There exists a considerable difference of opinion about the treatment of hyponatremia. Hyponatremia commonly follows the excessive administration of sodium free fluids. This is more suitably treated by the restriction of water rather than by the administration of sodium. When hyponatremia develops as a result of loss of sodium by vomiting, diarrhea, or excessive sweating, there can be no question that such sodium deficits should be replaced. When sodium deficit and metabolic acidosis coexist, it is advisable to replace the calculated sodium deficits with both hypertonic sodium chloride and sodium bicarbonate. Because of the ever present danger of precipitating pulmonary edema, such sodium deficits should be replaced cautiously. In some instances hyponatremia will develop although there is no evidence of exogenous loss or overhydration. In such instances, and when serious hyperkalemia (serum potassium above 7 mEq. per liter) is not present, we have not attempted to correct the hyponatremia. Moreover, diuresis is not inhibited by low levels of serum sodium. Diuresis was noted to occur in several patients when the serum sodium was below 126 mEq. per liter. In one patient the diuretic phase began when the serum sodium was 117 mEq. per liter.

Therapeutic measures to lower the extracellular level of potassium are indicated when the serum concentration of this ion has reached levels of 6.0 mEq. per liter. In some instances the simple addition of regular insulin to the 50% glucose (one unit per three grams of glucose) will be sufficient to lower the serum potassium and restore electrocardiographic abnormalities to normal (Figure 1). Such therapy may occasionally suf-

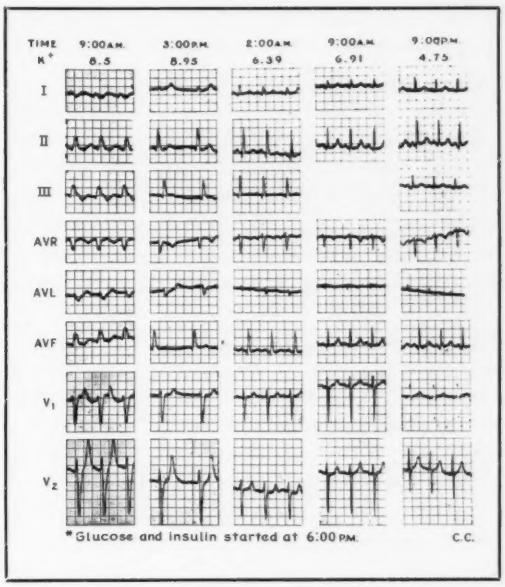

Figure 1. Effect of glucose and insulin on hyperkalemia and electrocardiographic abnormalities.

fice until the diuretic phase begins. On the other hand, if catabolic processes are marked, lowering of the serum potassium may be only transient. If the effects are transient and metabolic acidosis, hyponatremia, and hypocalcemia are contributing to the effects of the hyperpotassemia, calcium gluconate and sodium lactate may be given in the constant intravenous infusion as part of the daily fluid requirements. (Calcium gluconate and sodium bicarbonate cannot be added to the same infusion since calcium carbonate will be precipitated.) The correction of hypocalcemia may cause the electrocardiographic abnormalities to revert to normal even without changes in the concentration of the elevated serum potassium.[9] Potassium-free ion-exchange resins may also be given in a 10 per cent suspension as a retention enema. In the majority of cases, hyperkalemia can be controlled by judicious therapy during the course of oliguria. In those instances in which this is not possible, hemodialysis is the treatment of choice.

Treatment During the Diuretic Phase

The onset of the diuretic phase has been arbitrarily defined as that period during which urine volume exceeds 400 ml. per 24 hours. The urine volume generally increases by step-wise increments, but in an occasional patient there will be noted a sudden increase to two or more liters per day.

The guiding principle of therapy in the diuretic phase is the replacement of the excessive renal water and electrolyte loss Guides to the adequacy of such replacement are the body weight, the serum and urinary concentration of electrolytes, the urine volume, and the clinical signs of depletion of the plasma and extracellular fluid volumes. In the latter regard, the development of orthostatic hypotension and tachycardia in the sitting position may be a useful sign to indicate hypovolemia due to salt and water deficit. Hypokalemia may occasionally develop and should be corrected by the addition of potassium to the parenteral fluids. When moderate or severe metabolic acidosis is present, sodium replacement by both sodium bicarbonate and sodium chloride will facilitate correction of the acidosis. Parenteral fluids should be given slowly since too rapid infusion, especially in the early phase of diuresis, may precipitate convulsions or pulmonary edema.

Restriction of water may decrease the degree of diuresis but not abolish it. In one patient with carbon tetrachloride poisoning the fluid intake was intentionally limited to 2500 ml. per day for two days. The urine volume, however, was approximately four liters per day for those two days. Negative water balance was associated with increasing azotemia. In two other patients inadequate water and electrolyte replacement was associated with hypotension and tachycardia. It is apparent that, in these patients, the diuresis was due to the defective tubular reabsorption of water and not to the excessive production of metabolic water or overhydration during the phase of oliguria. If edema is present or clinical signs of overhydration are present it is obvious that the fluid prescription should permit the removal of this excess fluid.

When the early diuretic phase is well established and there are no gastrointestinal symptoms, a low protein, high carbohydrate diet may be instituted. This is generally well tolerated even if azotemia is still present. Later in the diuretic phase the protein content of the diet may be increased.

Prognosis

When acute renal insufficiency is uncomplicated by coexistent disease or injury, the prognosis is improved. Thus, in the present series two deaths occurred in 12 patients with carbon tetrachloride poisoning whereas 7 deaths occurred in the other groups of complicated acute renal insufficiency. Patients with acute renal failure secondary to chemical toxins appear to have a milder clinical course and to regain tubular discriminatory function more rapidly than do those patients with complicating disease or injury. Since recovery in the latter group is conditioned by the severity of the associated disease or injury, mortality statistics in various series are not comparable.

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DISCUSSION

DOCTOR CONRAD: Doctor Heller, in view of the acidosis in acute renal failure, why wouldn't hypertonic sodium lactate be preferable to hypertonic saline?

DOCTOR HELLER: If there is an exogenous sodium loss associated with fairly severe metabolic acidosis, I think indeed it would be better to give either sodium lactate or sodium bicarbonate along with the sodium chloride than the hypertonic sodium chloride alone. This poses another problem, and that is when

should be metabolic acidosis be treated? I don't know of any good answer to that other than to follow the pH if such is available, or to treat when the patient becomes symptomatic from severe metabolic acidosis. In such an instance, of course, life can be threatened by the acidosis per se, and so we have played it purely by ear and have treated the metabolic acidosis by bicarbonate and saline when it has become essential.

DOCTOR CONRAD: Is the use of an oral or an intravenous fat emulsion of value in meeting caloric requirements and reducing protein breakdown in acute renal failure?

DOCTOR HELLER: Yes, I think it is. The difficulty of giving anything orally early is that most of these patients have nausea and vomiting. However, one of our patients with carbon tetrachloride poisoning was treated with the Borscht regime and had very little in the way of metabolic acidosis and a very smooth convalescence. In those patients who can tolerate oral fat, there is an indication that cellular breakdown can be diminished. The other part of the question dealt with intravenous fat. I have had no experience with intravenous fat at all.

DOCTOR RELMAN: I have had no experience, but a rapid calculation I made yesterday from the information Doctor Mueller gave us would suggest that if you want to get the most possible calories for the least possible volume, 50% glucose solution would be better than the solution he described to us yesterday. There would be slightly more calories per cc in 50% glucose.

DOCTOR CONRAD: Doctor Heller, there is a series of three questions here which relate to the treatment of acute renal insufficiency. The first is what is your opinion of intermittent peritoneal lavage as a means of therapy in acute renal failure? The second asks about hemodialysis in such a situation; and the third concerns the use of venosection and blood transfusions in acute renal failure with high blood urea nitrogen when dialysis is not available.

DOCTOR HELLER: I have had no personal experience with intermittent peritoneal lavage, but I think since dialysis has become available, this has been pretty well given up. The complications of peritoneal lavage are considerable. Infections were invariable and to those who have used it, posed considerable problems.

As to hemodialysis, I think there are real indications for this. I think the artificial kidney has proved its worth. One cannot compare mortality statistics in the various reports in the literature. For example, the mortality in the 85 cases reported by Swann and Merrill was over 46%. Not all of those cases were treated by hemodialysis. It is almost impossible to control the various variables in the individual cases. The patients may die from their primary disease even without the advent of acute renal insufficiency. Certainly hemodialysis can be life-saving in the event of hyperkalemia that is not responding to any other method of therapy.

If the questioner is suggesting venesection as a means of exchange transfusions, I think it has been fairly well demonstrated that this does not play any real part in the treatment of renal insufficiency.

As to transfusion of these patients, I think it has been demonstrated that they stabilize pretty well a level of hemoglobin of about 8 gm/100 ml. of blood. Transfusions carries with it increased plasma volume, with a threat of pulmonary edema, and moreover it carries with it increase in the serum potassium. I would not advocate transfusion of these patients who appear to tolerate their anemia fairly well.

I might comment for just one moment as to the so-called congestive heart failure. These patients, with the development of so-called congestive heart failure, have an increased venous pressure with a normal circulation time. This indicates that they have a high cardiac output. So far as I know, there are no physiologic data available on the function of digitalis in the congestive failure of patients with acute renal insufficiency. When digitalis is used, one should protect against the development of digitalis toxicity when these patients start to diurese or when they are subjected to dialysis.

DOCTOR CONRAD: Is it advisable to use insulin in connection with glucose in the treatment of acute renal failure?

DOCTOR HELLER: We have started using insulin with glucose when the serum potassium reaches 6.5 mEq/L. Whether it would make any difference if one used it throughout the course of renal failure, I don't know. We do use it routinely when the serum potassium reaches 6.5.

DOCTOR CONRAD: A member of the audience has made an observation concerning severe and resistant bacteremias in patients with acute renal insufficiency or acute tubular necrosis. He says in his experience this is one of the most serious problems in his patients and he wishes you to comment on whether or not you have observed such patients, and if so, what you do about it.

DOCTOR HELLER: Only one of the patients of the 25 that I presented had a staphylococcal bacteremia terminally. This was a postoperative patient and it originated in an intra-abdominal abscess. This has not been a problem in our other patients. It is true, however, that patients who develop this postoperatively do have poor wound healing and may develop infection on that basis. One of our patients, for example, had a fairly severe dehiscence of a wound; but other than that, we have not been troubled with various types of bacteremia.

The Recognition and Management of Fluid and Electrolyte Alterations in Surgical Patients

WILLIAM E. ABBOTT
HARVEY KRIEGER
STANLEY LEVEY

WITH THE IMPROVEMENT of techniques and the advent of antibiotics the mortality and morbidity accompanying surgical procedures have steadily decreased. However, the management of fluid and electrolyte problems in both medical and surgical patients still presents some difficulties. The confusions which exists in the minds of many physicians in regard to the proper way of managing fluid and electrolyte problems is based on the misconception that this type of therapy is complex, difficult, and is primarily dependent on the chemical findings in the blood and serum. Also some rather complicated laboratory procedures which have been employed to investigate these problems have been suggested for the clinical management of patients with fluid and electrolyte abnormalities. The following discussion is based on practical methods which can be used for recognizing and treating surgical patients primarily by bedside observations and examinations rather than by depending on the chemical laboratory or by doing complex metabolic balance studies.

Periodically over the past thirty years the blood count, hematocrit, whole blood specific gravity and plasma protein or electrolyte concentrations have been advocated as guides for correcting fluid and electrolyte imbalances. More recently the methods of determining the plasma or blood volume have been improved and simplified so that these measurements have also been advocated as a means of recognizing alterations in fluid balance. While all of these methods may be helpful in managing the patient, the data they provide may at times be confusing or fail to reveal fluid and electrolyte abnormalities.

The errors in the blood and serum chemical determinations are usually not due to improper analytical techniques but more frequently occur because of improper obtaining of specimens or not separating the cells from the serum soon enough. It should also be remembered that blood or serum concentrations do not give information as to the state of fluid, electrolyte or nutritional balance. The state of balance of the patient is only determined by measuring the intake of fluid and nutrients and checking this against the output of the same substances. Dehydrated untreated patients may show a high or even normal hematocrit, protein, sodium, potassium and chloride concentration. This occurs because the kidneys often maintain approximately normal blood concentrations in spite of the fact that dehydration and deficits of these substances may exist. Frequently patients with a low intestinal obstruction, an ileostomy or internal shifts of fluids and electrolytes may be markedly dehydrated without a significant change in their blood or serum chemistries.

When there is an increase in capillary permeability substances used for measuring plasma volume (dye or isotope) "leak" from the vascular compartments in abnormally large amounts and a false high value for plasma volume may be obtained when actually hypovolemia exists. Plasma volume studies are most valuable to denote changes when serial determinations are carried out. This is usually not feasible in therapeutic endeavors. Laboratory determinations can be of great assistance if the state of balance is estimated from the patients history and physical findings and assessed in light of the patients clinical course.

Management of fluid and electrolyte balance usually is quite simple when the composition and the magnitude of the internal shifts, external losses and the approximate daily requirements are carefully estimated. In the following discussion the ways in which these losses can be determined will be presented.

Normal Adult Intakes and Outputs—The water intake of a normal adult is about 2000 to 3000 ml. a day of which approximately one-half is in the form of liquids and the remainder is derived from the water which is contained in soft or solid food (800-2000 ml. per day) and the water of oxidation (200-500 ml. per day). The fact that solid foods are 60 to 95 per cent water is often over-looked and thus the intake of water in the form of solid foods is frequently not considered. While the intake of electrolytes may vary quite widely the average adult consumes about 80 to 160 mEq. each of sodium and potassium and from 150 to 280 mEq. of chloride. This intake of chloride, greater than either of the two cations, should be remembered in the management of patients with hyperchloremic acidosis following uretero-sigmoidostomies or renal disease.

Usually in a healthy individual ⅓ to ½ of the fluid and approximately 90 per cent of the electrolyte and nitrogen intakes are excreted by the kidneys each day. Normally an individual loses about 500 ml. of electrolyte-free water from the lungs and a comparable amount of water containing approximately 40, 5 and 25 mEq. per liter respectively of sodium, potassium and chloride in perspiration. These physiological losses and the concentrations of sodium, potassium and chloride in such fluids are summarized in Table 1 and shown schematically in Figure 1.

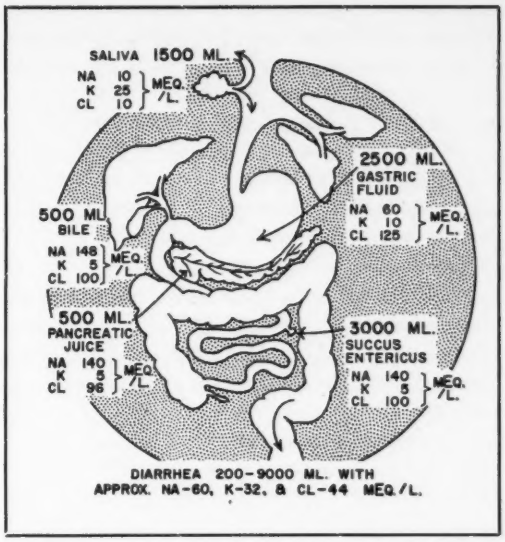

Figure 1. Daily physiologic losses of water and electrolytes.

NAME:_____ DIVISION:_____ HOSPITAL NO. _____

AGE:_____ YRS. HEIGHT:_____ WT.:_____ KG. DIAGNOSIS:_____

	SOURCE OF LOSS	APPROXIMATE LOSS VOLUME ML.	mEq./L. NA	K	CL	1. H_2O	NA	K	CL	2. H_2O	NA	K	CL
BASIC	LUNGS	400-1600	0	0	0								
	SWEAT	400-6000	40	5	30								
	URINE	0-3000	2-200 mEq.										
GASTRO INTESTINAL	GASTRIC	100-4000	60	10	130								
	BILE	80-800	145	5	95								
	PANCREAS	100-800	140	5	75								
	DUODENUM	100-2000	140	5	80								
	DUODENUM WITH GASTRIC	100-3000	135	5	100								
	ILEUM	100-9000	140	5	100								
	COLON	100-9000	80	30	40								
	TRANSUDATES AND EXUDATES	100-9000	140	4	100								
	TOTAL												
	BLOOD	500-5000	REPLACE VOL. FOR VOL. _____ ML.							_____ ML.			
	CALORIES (INCLUDING N)	KG. WT. _____ X 30 = _____ APPROXIMATE DAILY CALORIC NEEDS											
	NITROGEN WT. X 0.2 X 6.25 = DAILY PROTEIN NEEDS	KG. WT. _____ X 0.2 = _____ APPROXIMATE DAILY NITROGEN NEEDS											
	VITAMINS	2 TO 10 TIMES MINIMUM DAILY REQUIREMENTS											

Table 1. Work sheet for calculation and tabulation of water and electrolyte requirements.

Since fluid and electrolyte balance is altered by an inadequate intake, normal and abnormal external losses, and internal translocations of fluid and electrolytes, these three categories will be discussed separately.

Inadequate Intake—The oral intake of fluid and electrolytes may be inadequate in an adult patient who has psychiatric difficulties or in other individuals who are not willing or not permitted to consume sufficient amounts of nutrients. Although patients may have a reduced intake of food and fluid their caloric needs are not significantly decreased for several days thus they obtain energy by metabolizing fat and protein from their body tissues. Under these circumstances the insensible fluid and electrolyte losses continue and may even be accelerated if there is a fever and/or respiratory abnormalities. The kidneys may aid in the conservation of water and elec-

trolytes but often following an injury or during an illness the large amounts of nitrogenous waste products and acids which must be eliminated via the kidneys induce an obligatory loss of water. It therefore is necessary for the physician to supply the patient with the basic needs of water and electrolytes during many illnesses and following certain operations and injuries.

External Losses—Normally approximately 1500 to 2500 ml. of sensible and insensible fluid are lost each day. The external losses of fluids and electrolytes may be greatly increased in certain conditions such as excessive perspiration, vomiting, diarrhea, and drainage from wounds or from tubes in the gastrointestinal tract and from fistulae. It should be remembered that some times very large volumes of perspiration may be lost. There are instances on record where from 2 to 10 liters of fluid are lost from this source per day. The daily losses and concentrations of electrolytes in the gastrointestinal fluids which on occasions may also be lost externally are shown in Figure 2.

Although the chemical make-up of these fluids may vary the concentration of the electrolytes contained in the perspiration, saliva, and gastrointestinal fluids are approximately equal to the values shown in

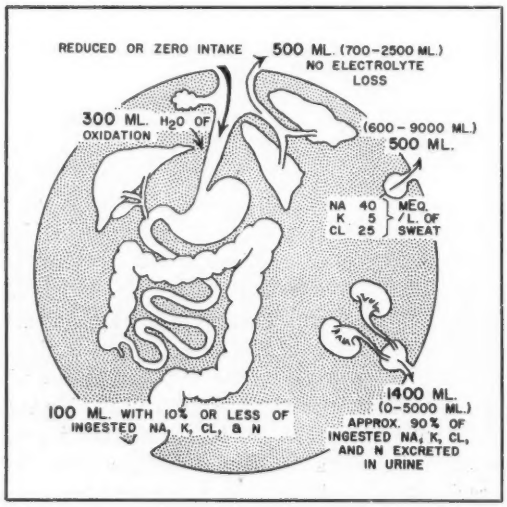
REDUCED OR ZERO INTAKE
500 ML. (700–2500 ML.)
NO ELECTROLYTE LOSS
300 ML. H2O OF OXIDATION
(600 – 9000 ML.)
500 ML.
NA 40
K 5
CL 25
MEQ. / L. OF SWEAT
1400 ML. (0–5000 ML.)
APPROX. 90% OF INGESTED NA, K, CL, AND N EXCRETED IN URINE
100 ML. WITH 10% OR LESS OF INGESTED NA, K, CL, & N

Figure 2. Gastrointestinal fluid and electrolytes which may be lost externally.

Figure 2. The concentrations of electrolytes in sweat and saliva are considerably lower than in the extracellular fluid. It also should be noted that the concentration of potassium is higher in saliva than in many of the other fluids and that there are no electrolytes present in respiratory water. In many instances mixtures of gastric and duodenal secretions as well as fluid from the lower small intestine and translocated fluids have a concentration of electrolytes comparable to that of extracellular fluid. Therefore considerable quantities of these types of fluids can be lost without producing a significant change in the plasma or serum electrolyte concentrations. When a patient vomits profusely or has lost fluid by drainage from the upper gastrointestinal tract, the kidneys will frequently excrete large amounts of sodium and potassium in order to compenstate for the excessive chloride loss in gastric fluid. In this way the acid-base balance or pH is maintained in spite of increasing dehydration and relatively normal serum electrolyte concentrations may exist. It is therefore necessary to provide both cations and anions in treating patients who have lost both fluid and electrolytes. When chloride is lost in the vomitus or drainage the patient should be given both sodium and potassium chloride. When there are losses of bile and pancreatic juice, which may contain large concentrations of bicarbonate, it is important to prevent hyperchloremic acidosis by the administration of sodium or potassium bicarbonate, citrate, gluconate or lactate. In patients with pyloric obstruction due to a peptic ulcer or in other individuals who lose large amounts of free hydrochloric acid by vomiting or gastric tube suction, the need for large amounts of chloride in conjunction with smaller amounts of both potassium and sodium should be obvious. Not frequently patients with peptic ulceration will show gastric fluid sodium concentrations which range from 30 to 60 mEq. per liter and at the same time because of a large amount of free hydrochloric acid will have a gastric fluid chloride level ranging between 125 and 150 mEq. per liter. It should be remembered that the primary source for large external losses of potassium is through the kidneys. Since the sodium concentration of lower smaller intestinal secretions

and of transudates and exudates is similar to that of the plasma, or extracellular fluid, the external loss of such fluids may greatly reduce the circulating plasma volume. The need for fluid with a chemical composition comparable to that of interstitial fluid in conjunction with a small amount of free water may be determined from the history, blood pressure, pulse, rate of urine flow and examination of the patient. It may frequently not be apparent from the laboratory findings alone.

Internal Shifts of the Body Water and Electrolytes (Formations of a Third Body Fluid Space)—Internal shifts of water and electrolytes occur following injury, infection, partial or complete obstruction (mechanical or neurogenic) of the gastrointestinal tract or venous circulation. These shifts may also occur when there are abnormalities in endocrine function, and in patients with cardiac, renal or hepatic disease. Maintenance or increase of body weight in a patient who has an inadequate caloric and protein intake indicates that he has retained significant quantities of fluid and electrolytes (third space).

Frequently shifts of fluid and electrolytes can occur quite rapidly so that an individual who appears well can be hypotensive and oliguric within a very short period of time. The rapidity and extent of this translocation of fluid into the "third space" is demonstrated by the case history of a twenty-six year old patient who was admitted to the University Hospitals of Cleveland several years ago. Five hours prior to admission he was in excellent health, having worked daily and had no interference with his normal food and fluid intake. He was awakened by severe intermittent cramping abdominal pains at about 3:00 a.m., vomited approximately 250 ml. of bile stained fluid, and shortly afterward came to the hospital where he again vomited a small amount of fluid. His temperature was slightly subnormal, pulse 120, blood pressure 82/50 and white count 16,500. The patient passed only a small amount of urine with a specific gravity of 1.028 and containing a slight trace of albumin. Because of small urine volume he was catheterized and no residual urine was found in the bladder. The patient was then given a 5 per cent dextrose solution in saline because he had been markedly oliguric for several hours, and this was followed by a 10 per cent dextrose solution in water to which small quantities of sodium lactate had been added. The presumptive diagnosis was a strangulated intestinal obstruction and a laparotomy was carried out. A volvulus of the small intestine around an inflammed Meckel's diverticulum was found. Approximately 700 ml. of serosanguineous fluid was removed from the peritoneal cavity. Because of the marked distention of the small intestine decompression was carried out by inserting a sump metal suction tube into the lower jejuneum near the junction of the ileum just above the point of obstruction. Over four liters of fluid was removed from the small bowel and it was noted that considerably more fluid was present in the intestinal wall, mesentery, and in the upper gastrointestinal tract proximal to the point which could be decompressed. It was believed that this patient had translocated and lost externally somewhere between 9 and 10 liters of electrolyte containing fluid in a period of about 12 hours. The intraperitoneal and intestinal fluid and that present as edema contained approximately 136 mEq. of sodium, 4 mEq. of potassium and 100 mEq. of chloride per liter and was equivalent to 7 to 8 liters of extracellular fluid. A total of 10,000 ml. of fluid was given to the patient from the time of admission until two hours postoperatively. This consisted of 1500 ml. of whole blood, 2,000 ml. of a 10 per cent dextrose solution and the remainder a 5 per cent dextrose solution which contained sufficient sodium chloride and sixth molar sodium lactate to provide about 135 mEq. of sodium per liter of fluid. His pulse rate decreased, blood pressure stabilized at a normal level, and urine flow increased after this quantity of water and electrolytes was given.

Figures 3, 4, and 5 depict schematically situations in which there may be a significant translocation of fluid and electrolytes from the normal body compartments. These are peritonitis, closed loop obstruction (sigmoid volvulus) and the shift of water and electrolytes into the small intestine during

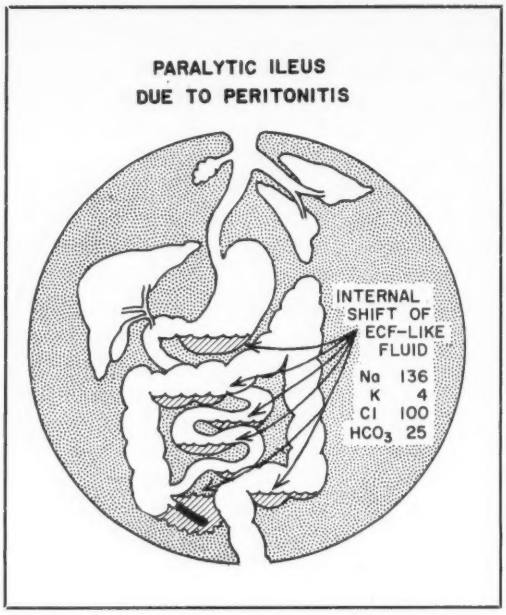

Figure 3. Internal shifts of fluid and electrolytes associated with peritonitis.

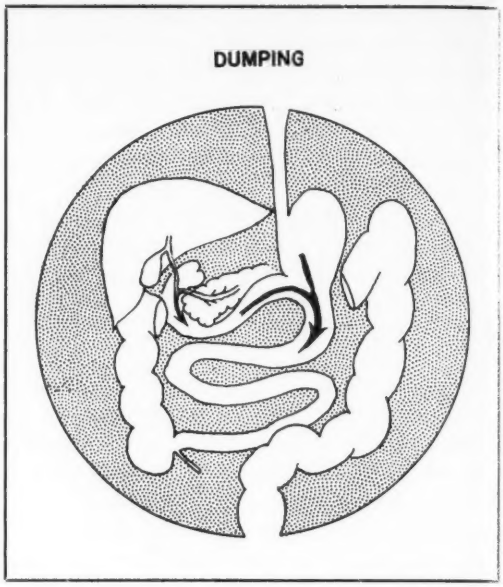

Figure 5. The internal shift of abnormal amounts of water and electrolytes which occurs during dumping.

Thus by estimating the magnitude of the patient's losses and sequestrations of fluid and electrolytes and at the same time considering the amounts of these materials required to meet the deficits plus the basic needs (insensible losses and urine formation) one can readily calculate the quantity a "dumping" attack following a gastric operation.

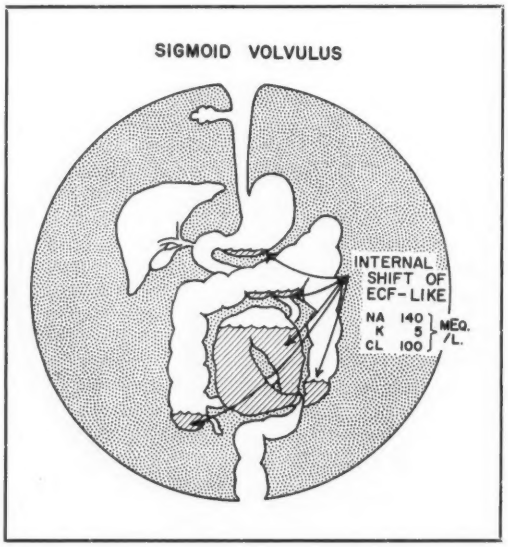

Figure 4. Third space formation (internal shift of water and electrolytes) associated with a sigmoid volvulus.

and composition of replacement needed. Using a scheme similar to that presented in Table 1, one can tabulate all losses and readily calculate the amount of replacement fluids. While the amount of fluid and electrolytes lost by external drainages or vomitus can be quite accurately measured, it is more difficult to determine the losses resulting from oozing of denuded surfaces or the magnitude of the third space. However, by periodic evaluation of the patient's response to therapy (thirst, eye ball tension, skin turgor, pulse rate, venous and arterial pressure and the rate of urine flow) it is usually possible to provide any necessary adjustments in intake. With this method of treating fluid and electrolyte aberrations one uses the concepts of simple chemical bookkeeping (balancing total losses against intake) rather than depending completely on complex laboratory procedures.

DISCUSSION

DOCTOR DuVAL, Associate Professor of Surgery, University of Oklahoma School of Medicine: Doctor

Abbott, have you found the sodium content of pancreatic juice to be fairly constant or would you advise measuring this concentration at intervals?

DOCTOR ABBOTT: We haven't had the opportunity to measure the sodium concentration in pancreatic juice too often. We did have a patient with a pure pancreatic fistula not long ago, and for the most part, our results showed that the sodium concentration is near isotonic with the extracellular sodium concentration. Others have also shown that following stimulation of the pancreas the chloride concentration of the pancreatic fluid drops to well below that normally found in plasma, while the bicarbonate concentration may rise from around 30 mEq/liter to a concentration which is two or three times as high as that in the resting gland. I'm not sure how the electrolyte concentrations are affected by disease. It would be very interesting to collect some of the pancreatic juice that Doctor DuVal and others obtain following pancreatic drainage procedures in patients with chronic pancreatitis.

DOCTOR DuVAL: In such studies as you have done have you found that there seems to be a discrepancy between your findings on volume output of pancreatic juice per day as compared to what is being currently reported in textbooks?

DOCTOR ABBOTT: Yes, I believe there is quite a difference. I think we were all taught that the normal individual secretes about eight to ten liters of fluid into the gastrointestinal tract each day, and I am sure, as Doctor John Peters emphasized many years ago, that it takes food and water to stimulate gastrointestinal secretions; and therefore, if little or no food and water are consumed, the volume of digestive juices would be greatly reduced. As soon as patients are taken off of everything by mouth, our studies indicated that the output of saliva, gastric secretions, bile, pancreatic juices, and succus entericus are greatly diminished. More recently we have been removing gastric suction tubes in 12 to 24 hours from postgastrectomized patients, keeping them off of everything by mouth, and periodically measuring any retained fluid if it sems necessary. We have been surprised to find very little fluid. I believe that it is important to remember that the amount of gastrointestinal fluid secreted, including pancreatic juice, fluctuates a great deal. Usually the secretion is more plentiful following the ingestion of food or water than that occurring in the patient who is not eating or drinking.

DOCTOR DuVAL: A question that has been posed on several occasions involves the preparation of a patient for surgery who has pyloric obstruction. I'd like to know if the losses are substantially different with constant suction, on such a patient, as opposed to letting the patient take fluid by mouth and emptying the stomach once or twice daily? Is there a difference in the losses with those two ranges of management?

DOCTOR ABBOTT: Yes I think there is considerable difference. Recently, we had a patient who insisted upon treating herself. We let her manage her oral intake while intermittently her stomach was emptied by a gastric tube. In this patient, we were able to make some observations of this type. When a person takes food and water, they secrete more digestive juices into the gastrointestinal tract. It's not really the water that the patient ingests that you worry about losing by suction, but the water and electrolytes that the patient secretes in response to the water they swallow. We don't believe that there is ever a need for an emergency operation in patients with pyloric obstruction, they should all be well hydrated and the acid-base balance and nutritional deficits should be corrected or restored toward normal before an operation is undertaken.

DOCTOR DuVAL: Would you discuss the problem associated with the electrolytes that have been badly deranged and then returned to normal, at which time the patient dies.

DOCTOR ABBOTT: I am glad that you touched on this problem, since the point I would like to make, and the point which I tried to make during my talk, is that a plasma or serum electrolyte concentration per ce measures only one dimension. It represents only concentration and gives no indication as to the total quantity. Obviously, we need a three-dimensional view, volume plus concentration, to be accurate. As McIver and Gamble emphasized so well in an article published in the Journal of the American Medical Association in 1927, if one lined up ten liters of saline solution and took a sample of fluid from any one of these bottles, the concentration would be the same. However, if somebody came along and knocked over and broke three of these liter bottles, the concentration in the remaining seven liters would still remain the same, although the total amount of water, sodium, and chloride has been decreased by 30 per cent. In a sense, this is what is happening in a patient after a thermal burn and in a patient with internal shifts into the peritoneal cavity and the other regions. He is losing fluid into a traumatized or inflamed area which has an electrolyte concentration exactly the same as that of plasma. Unless he starts sweating and breathing fast and losing water, which would tend to raise his serum electrolyte concentration, or unless we pour a lot of fluid which is low or free of electrolytes into him, which will lower the plasma electrolyte concentrations, his electrolyte values will remain at a relatively normal concentration. It is very disturbing to have somebody say that they have followed a patient who came to autopsy and he was in good fluid and electrolyte balance, since his serum concentrations were essentially normal. Yet, if you check the patient's intake or output, it becomes obvious that this aspect has been overlooked. It should therefore be remembered that balance of water or electrolytes can be determined only after careful intake and output studies and need not have any relation to the serum electrolyte concentrations.

A Practical Guide to Fluid Therapy in Burns

CURTIS P. ARTZ

THE PRIMARY DERANGEMENT after burn injury is loss of fluid from the intravascular compartment brought about by vaso-dilatation and increased capillary permeability. This loss of fluid leads to a diminution of the circulating blood volume and thereby the threat of so-called "burn shock." The amount of fluid lost varies with the extensiveness of the burn. Some fluid passes into the interstitial space, as is evidenced by edema formation. Additional fluid is lost as exudate into blisters and from the weeping surface of partial thickness burns.

Proteins, electrolytes and water pass from the plasma into the interstitial space immediately after the burn (Figure 1). Colloid, electrolyte solution and water must be given to maintain an adequate circulating blood volume and thus prevent hypotension. Some of this replacement therapy passes through the damaged capillary walls into the interstitial space, giving the patient an expanded interstitial space and thereby a combined load of water and sodium (Figure 2).

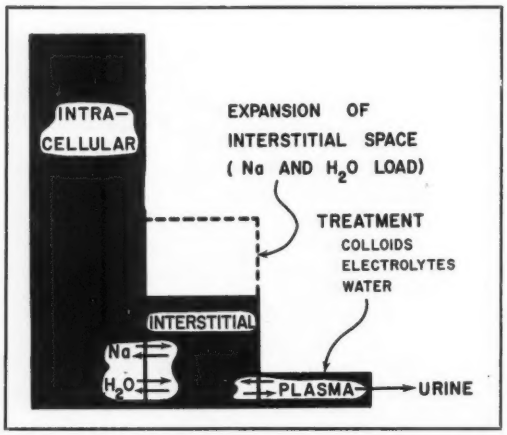

Figure 1. Diagram of body water compartment changes after burns. Soon after the injury plasma passes into the interstitial space. Treatment with colloid, electrolytes and water maintain the plasma volume but water and sodium continue to flow into the interstitial space. This expands the interstitial space as is shown by the dotted line. The increased amount of sodium and water in this interstitial space means that the patient has a combined load of sodium and water. This remains until redistribution of fluid occurs. There is an interchange of sodium and water between the intracellular compartment and the interstitial space, but this is not well defined. After the third day the interstitial space decreases in size and water is usually excreted faster than sodium.

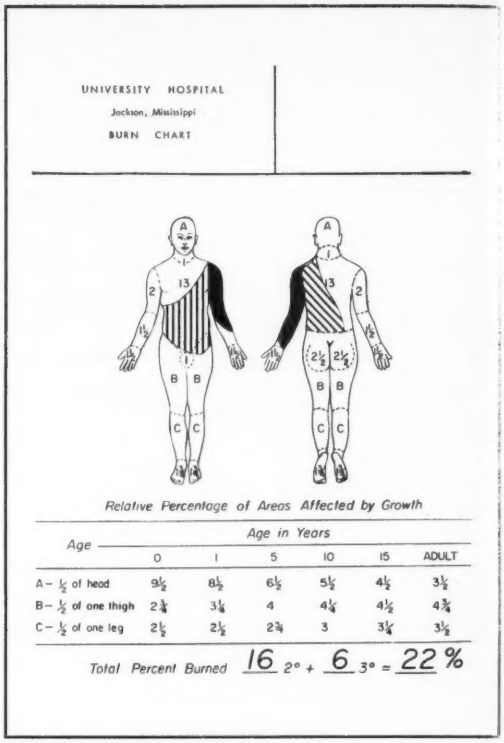
UNIVERSITY HOSPITAL
Jackson, Mississippi
BURN CHART
Relative Percentage of Areas Affected by Growth
Age in Years
Age 0 1 5 10 15 ADULT
A– ½ of head 9½ 8½ 6½ 5½ 4½ 3½
B– ½ of one thigh 2¾ 3⅛ 4 4¼ 4½ 4¾
C– ½ of one leg 2½ 2½ 2¾ 3 3¼ 3½
Total Percent Burned 16 2° + 6 3° = 22 %

Figure 2. Typical hospital sheet with Lund and Browder chart. On this sheet is sketched the second degree (vertical lines) and third degree (solid black) areas of burn injury. This is the most accurate method of determining percentage of body surface burned.

This load slowly increases as treatment is being given until about 48 hours after the burn. At that time capillary permeability diminishes and fluid redistribution begins. Water and sodium are reabsorbed into the vascular system, and the interstitiitial space decreases. Excess sodium and water are excreted by the kidneys. In extensive burns it may take several days for this expanded interstitiitial space to return to normal.

The loss of red blood cells following burns has been studied extensively.[1,2] There is a loss of red blood cells after a deep burn because:

a) Many cells in the burned area are destroyed directly by heat.

b) Delayed hemolysis occurs for 24 to 48 hours after burning.

c) Thrombosis occurs in the capillaries beneath the burned tissue and causes a decrease in the red cell mass.

d) Many red blood cells are lost following sludging of blood.

From a clinical standpoint it can be assumed that at 10% to 15% of the red cell mass is destroyed in any appreciable third degree burn.

The desirability in initial therapy is to provide enough colloid, electrolyte solution and water to maintain an adequate plasma volume without giving excessive replacement therapy that may overexpand the interstitial space.

Initial Evaluation

Unlike most patients who suffer shock, burned patients have predictable losses. The size of the patient and the extent of the burn permit an estimation of the amount and rate of fluid loss. The aim in initial management is to estimate this fluid loss and replace it as it is being lost, thereby preventing hypotension.

Several methods have been devised for estimating the extent or percentage of body surface burned. The most common method is the familiar "Rule of Nines."[3] This formula is easily remembered and very convenient, but it is not as accurate as the use of a Lund and Browder Chart (Figure 2).[4] Every hospital should have a Lund and Browder Chart on a record sheet available for use in the emergency room. By marking the burned area on this chart, one is able to estimate rather accurately the percentage of body surface burned.

At the same time that the percentage of burned area is being determined, an attempt should be made to estimate the relative amounts of second and third degree injury. Although the total volume of fluid required is about the same for second degree as for third degree injury, the type of fluid given is somewhat different. Patients who have primarily second degree burns can be adequately resuscitated with plasma, or a plasma volume expander, and electrolyte solutions. Patients who have appreciable amounts of third degree injury require additional whole blood.

Planning the Method of Intravenous Administration

Since the life of a burned patient depends on the infusion of replacement therapy, it is wise to plan initially the utilization of various routes of administration. In the extensively burned patient intravenous fluid is often required for ten to twelve days. During this time phlebitis and thrombosis may occur in several veins necessitating a change in infusion site from one vein to the other. Good veins for intravenous infusion may be difficult to find; therefore a plan for saving veins should be worked out before therapy is instituted.

As soon as the patient is admitted, a large gauge needle should be placed into any accessible vein and blood drawn for cross matching and a base-line hematocrit determination. An infusion of Dextran or lactated Ringer's (Hartmann's) solution should be started through the same needle. This will permit infusion of fluids until there is time to sit down and plan the steps in therapy.

If it is determined that prolonged intravenous therapy will be necessary, a cut-down must be performed. The cut-down cannula is inserted into a vein of any available extremity as distal as is practical. If thrombosis of the vein occurs, then the cannula can be moved proximally. If there is a burn of the upper portion of the body, the cut-down should be inserted into an ankle vein. If phlebitis occurs, this can be changed to the opposite ankle vein or an upper extremity vein if available. Should thrombosis occur in this area, a vein higher on the leg can be cannulated, and eventually a femoral catheter may be necessary. The use of a

percutaneous plastic femoral catheter is very advantageous; however, this method of intravenous administration should be saved as a last resort. If thrombosis occurs in the femoral or iliac vein, then the other veins of that extremity will not be suitable for use. The femoral catheter should not be left in place for more than seven days because of the fear of thrombosis and possibly embolism. In very extensively burned patients, particularly when all four extremities are injured, it may be necessary to give infusions initially by way of a femoral catheter. When this occurs, the catheter should be inserted in one side and allowed to remain for seven days, then moved to the other side.

Planning the Amount of Fluid Therapy

As soon as the initial procedures in the care of the patient and the assessment of injury are made, the amount and type of fluid therapy should be planned. Several factors influence the plan:

a) Extent and depth of burn

b) Weight of the patient

c) Presence of respiratory irritation

d) Age of patient

e) General physical status of the patient.

By the use of a fluid formula it is possible to estimate from the weight of the patient and the extent of body surface burned the approximate fluid requirements for the first 48 hours. In the patient who has inhaled noxious gases there is the danger of pulmonary edema, and therefore, somewhat less than the usual estimated amount of fluid therapy should be given. Likewise, elderly patients and patients with severe cardiovascular disease should be given minimal replacement therapy.

Usually intravenous fluids are required only in burns of more than 20% of the body surface. Occasionally, burns that are primarily full thickness or burns in children, although less than 20%, may require intravenous therapy. Most minor burns, however, can be treated by oral fluids. A salt and soda solution provides the most satisfactory method of replacement. This solution is prepared by dissolving 3 grams of salt (½ teaspoonful) and 1.5 grams of bicarbonate of soda (½ teaspoonful) in a quart of water. This solution is tolerated better when given cold and flavored with lemon. It is a hypotonic solution with approximately 70 mEq. of sodium per liter. If vomiting occurs with oral electrolyte solution, then lactated Ringer's may be given intravenously in amounts of 2 cc. per kilogram for each per cent of burn.

In the more severely burned patient well planned and well regulated intravenous therapy is required. Many patients with such extensive burns that there is little chance of ultimate survival live for several days. If therapy is to be successful, advantage must be taken of the more or less predictable volume and rate of fluid losses. In this respect the physician has a therapeutic opportunity that is rarely encountered in other diseases characterized by disturbed water and electrolyte distribution. If judicious treatment is instituted within a few hours after injury, signs and symptoms of derangement can frequently be prevented. Because the volume and rate of fluid losses are predictable, several fluid formulas for estimating the amount and type of therapy have been devised. All seem to have merit. The Brooke formula has proved to be most successful in a very extensive experience.[5] This formula calls for the following fluids in the first 24 hours after injury:

a) Colloid (blood, Dextran or plasma)—0.5 cc. per kilogram for each per cent of body surface burned

b) Electrolyte solution (lactated Ringer's)—1.5 cc. per kilogram for each per cent of body surface burned

c) Water requirement (dextrose in water) Adults—2,000 cc.

Water requirements in children vary. The

following is a rough guide to daily water requirements in infants and children:

a) During the first two years—120 cc. per kilogram

b) Second to fifth year—100 cc. per kilogram

c) Fifth to eighth year—80 cc. per kilogram

d) Eighth to twelfth year—50 cc. per kilogram.

Burns of more than 50% of the body surface should be calculated as 50% burns.

The above formula is only an *estimate* of fluid requirements, which allows a *plan of therapy*. The exact amounts of fluids given should be in accordance with the response of the patient. It is usually anticipated that ½ of the above fluid requirements should be given in the first 8 hours, ¼ in the second 8 hours, and ¼ in the third 8 hours. This rate of administration is based on the fact that fluid losses early after the burn are more rapid than later.

The depth of burn influences the type of fluid therapy, particularly in the colloid requirement. Second degree burns up to 40 per cent of the body surface will do well if the colloid requirement is met by the use of Dextran or plasma. Burns that have an appreciable amount of third degree injury should be given the colloid requirement as half Dextran and half whole blood. The protein content of plasma would favor it as a therapeutic tool; however, it is considerably more expensive and virus-free plasma is not a readily available as is Dextran. Most clinicians, therefore, prefer Dextran to plasma as initial colloid therapy.

Physiologic saline solution is used extensively as an electrolyte requirement. It is inexpensive and readily available. Its chief drawback is the excessive high concentration of the chloride ion. Burned patients have a tendency toward metabolic acidosis, and massive infusions of physiologic saline solution are followed by hyperchloremia, which tends to enhance the acidosis. A balanced electrolyte solution, such as lactated Ringer's, is more acceptable. When lactated Ringer's is not available, a satisfactory electrolyte solution containing 159 mEq. of sodium and 103 mEq. of chloride per liter can be prepared by mixing physiologic saline solution and 1/6 molar lactate solution in proportions of two volumes of saline to one volume of 1/6 molar lactate.

In some patients the water requirement may be given orally. Most severely burned patients, however, develop a paralytic ileus early, and vomiting may result. It is usually safer to withhold all fluids in a seriously burned patient and give the entire water requirement during the first 24 or 48 hours by the intravenous route.

As soon as the plan of fluid therapy has been determined, it should be written down, but it is expected that it will be changed. As Doctor Francis Moore has so aptly put it, "Planning fluid therapy in the early burn is like a family budget. It is made to be broken."[6] As the plan is followed, the actual amount administered is dictated by the clinical response of the patient. It is foolhardy to think that fluids can be estimated and ordered on a 24 hour basis. There is no substitute for hourly observation. The type of therapy and rate of infusion must be changed frequently in accordance with the patient's response.

Following the Plan of Therapy

To follow the fluid therapy adequately in a burn of more than 25% of the body surface, it is absolutely manditory that an indwelling catheter be placed in the bladder so that the hourly output of urine can be measured. It should be removed, however, as soon as possible, or urinary tract infection may develop. After the initial cutdown has been performed, and an adequate amout of plasma volume expander, blood, or lactated Ringer's has been given, attention should be directed toward local care. Anesthesia is unnecessary and contraindicated. As soon as the local burned wound

has been treated and the patient has been taken to the ward, a plan for following fluid therapy should be outlined. If several physicians are assisting with the care of the patient, one should be delegated as having the primary responsibility of writing orders and determining the speed and type of fluid administration. A chart should be prepared to record hourly urinary output, blood pressure, and intravenous infusions.

In general most of the colloid requirements should be given early. This will help in maintaining an adequate plasma volume and prevent hypotension. If the patient has had no fluid therapy for several hours between the time he is burned and the time of admission, very energetic colloid and fluid therapy may be necessary. In very severe burns there may be no urinary output for a few hours. During this time energetic colloid and electrolyte therapy should be given. Once the urine has started to flow, it can be assumed that the intake is catching up with the losses from the vascular tree. After observing the urinary output for a few hours, a good estimate of the rate of infusion can be made.

The chief value of the estimated fluid requirements by the use of a formula is that it allows knowledge of the ratio of colloid to electrolytes to dextrose and water. As the response of the burned patient is determined, a fall in blood pressure with fall in urinary output means additional colloid therapy. A fall in urinary output with a stable blood pressure means that additional electrolyte solution or water is required.

The patient's response must be re-evaluated every hour or two and fluid intake regulated. After 8 to 12 hours it may be possible to predict what will be necessary in the way of intake, and observation then can be less frequent.

One of the great dangers that occur in early fluid therapy of burns is excessive intake. It is not uncommon for a physician to assume that 30 cc. per hour urinary output is good, but 50 to 100 cc. is better. This is a dangerous fallacy. The aim in early fluid administration is to give the least possible amount that will assure a plasma volum sufficient to maintain a pressure in th glomeruli adequate for the output of urin Additional fluid therapy leads only to adde expansion of the interstitial space. Exces water and electrolytes in amounts that wi produce a urinary output of 50 cc. or mor per hour will lead to overexpansion of th interstitial space. This means an increase load of sodium and water. A urinary ou put of 15 cc. per hour is an indication fo more rapid therapy, and an output of 50 c per hour should be followed by a reductio in rate of administration.

In infants, elderly patients, and patient with hypertensive vascular disease or irri tation of the respiratory tract, the urinary output should be kept at 10 to 15 cc. per hour. In modern day treatment of burns excessive fluid therapy is a more common error than inadequate fluid therapy. Restlessness is usually a sign of inadequate therapy. In almost all burned patients there is a tremendous thirst which disappears in the well hydrated patient in 12-18 hours.

At times when the blood pressure is normal, additional colloid therapy may not result in a satisfactory output of urine. When such an event occurs, colloid therapy should be discontinued and electrolyte solutions of water given. By following the urinary output and the blood pressure, one is able to determine whether the change in urinary output is due to a lack of fluid, specifically water, or due to a diminished plasma volume with an inadequate flow of the renal glomeruli.

In patients with burns of the head occasional cerebral edema may occur during the course of treatment. This phenomenon is more common in children. To prevent this disastrous complication it is necessary to follow the temperatures carefully during the first 48 hours. An unusual temperature rise to 104° in a well hydrated patient may mean the beginning of cerebral edema. The eye grounds should be observed, and if there is any evidence of edema, the infusion of fluids should be decreased immediately. The mechanism of formation of cerebral

edema in burned paients has not been explained.

During the second 24 hours, the patient will require the same amount of water and about one-half the colloid and electrolyte requirement of the first 24 hours. Laboratory determinations during this period are of little value and are unnecessary. During the second 24 hour period, the ratio of colloid, electrolyte solution, and water should be calculated and administered according to the urinary output.

Therapy After Forty-Eight Hours

At 48 hours wound edema is maximal and at this time fluid redistribution occurs. Usually water and sodium return to the vascular system and the urinary output increases. In moderate burns the patient will regulate his fluid needs by oral intake. In more extensive burns some of the fluid requirement may be taken orally and the remainder intravenously in accordance with the urinary output and the serum sodium concentration. In the very extensively burned patient it may be necessary to continue fluid by the intravenous route for several days.

After 48 hours the laboratory may be quite helpful in determining therapy. Careful observation should be made of the hematocrit and the serum sodium. If the hematocrit falls below 45, blood should be given. Hyponatremia is usually present in spite of a large sodium load in the interstitial space. A low serum sodium in injured patients, particularly in burn patients, is associated with a good clinical response and is desirable. The insensible water loss may be quite marked, up to 5000 cc. a day in an adult. After the acute stress of the burn injury the body has a tendency to hold on to sodium, and very little is excreted by the kidneys. The loss of water by the insensible route and by the urine may be considerably greater than the loss of sodium. This means that the water load is diminishing more rapidly than the sodium load, and therefore a rise in serum sodium may occur. A serum sodium of 145 mEq. per liter or more is an indication for additional water. When insufficient water is given, the serum sodium may give rise to a hypernatremia.[7] The increased concentration of sodium in the interstitial space leads to intracellular dehydration and sometimes death. Daily serum sodium determinations, therefore, are very important in the extensively burned patient, and water should be given to prevent hypernatremia.

After the first 72 hours potassium may be required. When the patient can take nourishing fluids and food orally, intravenous potassium therapy is unnecessary. In the more severely injured patient it may be necessary to give 80 mEq. of potassium a day by the intravenous route until the potassium requirement can be met by oral intake. Later in the postburn period intravenous therapy is required to maintain an adequate red cell mass and in some instances for additional protein therapy. When the patient is unable to take adequate proteins and calories orally, some type of intravenous protein, such as protein hydrolysate or plasma, may be necessary as a supplement. The hematocrit should be determined twice weekly, and an adequate amount of blood given to maintain a hematocrit of 45 or above in the well hydrated patient.

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DISCUSSION

DOCTOR DuVAL: Doctor Artz, with respect to Dextran, I'd like to ask two questions: What is the situation as you know it with respect to prolonged bleeding time associated with the use of Dextran? What do you currently recommend as the best plasma volume expander for standard use in an emergency situation in a small hospital?

DOCTOR ARTZ: There appears to be an increased bleeding tendency in some patients with large quantities, two or more liters, of Dextran. This change in bleeding time does not become clinically significant by increasing the amount of bleeding after injury unless a large quantity of Dextran is given. This does not occur in all patients. I have seen some patients bleed rather profusely after giving them about two liters of Dextran. On the other hand, I have seen many patients receive two and one-half liters of Dextran with no increase in bleeding. I believe that most people who use Dextran use only one liter or maybe a liter and a half. This certainly is safe, from a clinical standpoint.

Second, where do we stand with the plasma volume expanders? There may be some plasma volume expanders coming on the market that will be better than Dextran, but it is doubtful that this will occur for a long time. Plasma is still best, but it is difficult to obtain appreciable quantities in the virus-free form. It is also quite expensive. The gelatins have not been very effective.

I would say that Dextran is a fine plasma volume expander and should be used whenever a plasma volume expander is needed.

DOCTOR DuVAL: Doctor Artz, may I ask you quickly on behalf of at least a few people in the group, who I am sure would like to know, where can one obtain a copy of the Lund and Browder chart? Do you have a ready reference for this?

DOCTOR ARTZ: In two places: (1) Lund, C. C. and Browder, H. C. The Estimation of Areas Burned. Sug., Gynec., and Obst. **79:** 352, 1944, (2) Artz, C. P. and Reiss, E. The Treatment of Burns. Philadelphia, W. B. Saunders Co., 1957, p. 10.

DOCTOR DuVAL: May I ask you the question that has been posed by several people. The so-called third space in burns, unlike the third space as seen in bowel obstruction where we are removing fluid physically at one point or another during the course of therapy, brings up the question of the danger of treating a deficiency secondary to this translocation of the fluid. As the patient recovers and the translocated fluid returns to its usual locus, with over hydration and secondary hypervolemia, how do you determine that this is occuring? How do you manage the patient during this period?

DOCTOR ARTZ: First, I think that all injured patients and all people with difficulties in the gastrointestinal tract not only have losses to the exterior but losses into the peritoneal cavity, into the lumen of the bowel, into the bowel wall, and into the wall of the mesentery. This gives a **load** of sodium and a **load** of water. When fluid redistribution occurs, there is usually an increase in the urinary output. With this increase in output, the best method of measuring whether or not adequate amounts of water are being given is by determining the serum sodium. In other words, you choose not to over-hydrate the patient during this period. If his urinary output begins to increase, then you hope this is redistribution of the fluid. The only real worry is that he be given an adequate amount of water for insensible water loss. One looks at the patient, his surroundings, his fever, the temperature of the room, and tries to estimate the amount of water to replace his insensible losses. Then, if the serum sodium rises rapidly, electrolyte-free water must be given. The important thing is to estimate the insensible loss and try to replace it and not try to use the urinary output as regards to how much therapy should be given.

DOCTOR DuVAL: How about using marrow infusions? And while on that, you might just briefly state whether or not you feel there is any contraindication in using the same extremity as may be involved with the burn.

DOCTOR ARTZ: I'm not a real expert on sternal infusions of the bone marrow. A few years ago we had quite an experience for about a year attempting to infuse both the sternum and the tibia. For a few liters of fluid or for 500 milliliters of blood, it seemed to work well, but after that large volumes and quantities will not go in very well. At least, I've been unable to do it in my own experience. I think if one wants to give a unit of blood or maybe one or two liters of fluid and there are no other routes, that it is probably worth trying.

Secondly, I see no reason why one should not look down beneath the burned tissue for a vein. Sometimes if it is a full thickness burn, it is very difficult to find one. I think all of us have gone through burned tissue and inserted an indwelling polyethylene catheter. However, when one does this, you expect infection to go into the venous system and set up a bacterial as well as irritated type of thrombophlebitis, and this route does not last very long.

The Practice of Fluid Therapy

R. TARAIL

MANY OF OUR FAILURES in regard to fluid therapy are not the result of our failure to keep up with the latest advances. In a great many instances poor fluid therapy is little more than a failure of the physician, the nurse, and the hospital in quite another direction. Thus poor fluid therapy may occur because we don't activate long-established principles of good medical care as well as humane, diligent nursing and administrative practices. At the risk of belaboring what may seem to some to be a rather obvious point, I wish to emphasize this thesis further.

Please ask yourselves these questions. How often is the practice of fluid therapy impaired by inadequate history taking? How often is the practice jeopardized by hurried physical examination? How often is it given a black name by utterly inaccurate measurements of intake and output? How frequently do we neglect having accurate daily measurements of body weight? How often are our best intentions endangered by hospital chemical laboratories which lack professional supervision and which in many instances can be shown to be unreliable? How often is the successful practice of fluid therapy impaired by insufficient attention to underlying illnesses?

I shall try to concentrate our attention upon three commonplace aspects of fluid therapy: 1. Risks of air embolism; 2. The matter of how rapidly or slowly parenteral fluids should be given; and 3. The utility of accurate, daily measurement of body weight especially in bed fast patients.

Risks of Air Embolism

At least one catastrophe at our hospital pointed an accusing finger at the risks of cavalier attention to standard equipment used daily for giving blood transfusions. The familiar Y-type set (Figure 1) as emphasized by Kerr[2] is constructed with the built-in possibility of causing air embolism. Until Kerr's convincing demonstration of this possibility at our hospital I was ignorant of it. I am therefore bold enough to assume that this source of catastrophe has escaped the attention of many of you as well.

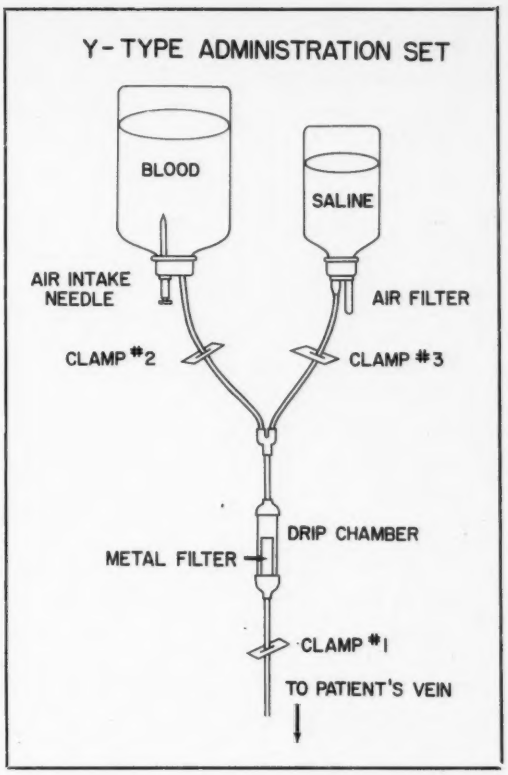

Figure 1. Practice of Fluid Therapy.

Assume for the moment that the Y-set picture in Figure 1 is intact and perfect in its manufacture and has no defects when used for transfusion. An infusion of blood is completed, and clamp No. 2 remains open, clamp No. 1 is completely open, and clamp No. 3 constricts the tubing and controls the rate of saline administration. *Under these circumstances large quantities of air can be shown to enter the tubing below the drip chamber at a rapid rate.* The source of this air is through the air-intake orifice of the empty blood bottle.

That this inrush of air occurs under the above-described circumstances is readily verified by anyone curious enough to spend a little time manipulating the controlling clamps. The explanation for this entry of air became clear to me through discussions

with a biophysicist at our hospital, Doctor Clinton Janney: It can be shown when the blood bottle is empty, clamp No. 1 and No. 2 open, and clamp No. 3 partially constricts the tubing so that the pressure in the lumen above clamp No. 3 exceeds atmospheric. In sharp contrast however the pressure in the lumen below constricting clamp No. 3 on the saline limb of the Y and below the junction with the blood side is distinctly less than atmospheric. These facts can be vividly verified by inserting a suitable needle into the lumen of the tubing above constricting clamp No. 3; this results in an outpouring of saline solution because the pressure within the lumen above clamp No. 3 is greater than atmospheric pressure. But if a needle is inserted into the lumen of the saline limb of the Y below constricting clamp No. 3, numerous bubbles of air can be seen to enter because the pressure within the lumen below clamp No. 3 is less than atmospheric. Air may enter from the empty blood limb of the Y because when clamp No. 2 remains open the pressure within the lumen of this limb is atmospheric (freely communicating through air intake needle) whereas the pressure at the junction of the Y (below constricting clamp No. 3) is less than atmospheric.

A special, perhaps less obvious, example of the same conditions develops if the blood bottle is empty, clamp No. 2 is open, and clamp No. 3 constricts the tubing to a greater extent than clamp No. 1. Again, large quantities of air may enter the tubing below the drip chamber rapidly and a similar explanation obtains.

A moral of this story is that after the blood has run in clamp No. 2 must obstruct the lumen completely, clamp No. 3 should be opened completely, and clamp No. 1 should constrict the lumen and control the infusion rate. Unfortunately the clamps of leading manufacturers do not readily lend themselves to easy assessment of just how much they constrict the lumen. All or none clamps, such as a spring clamp or hemostat at the upper limbs of the Y are far superior, and much less dangerous. And, incidentally, instead of the throw-away clamps provided at position No. 1 a well-made tunnel or screw-type clamp is desirable for rate control. Furthermore since, in a sense, an empty blood limb of the Y is precisely analogous to a needle poised to puncture the tubing, serious consideration of the advisability of abandoning Y sets appears to be in order.

Let us turn now to some of the risks of air embolism related to the use of defective sets for fluid administration. Holes may be present in the plastic tubing as a consequence of faulty manufacture, careless handling, or needle punctures. If the drip chamber and plastic tubing are fabricated as separate components there is danger of a leaky junction. Such defects may occur not only in Y sets but in single channel sets as well.

It can be readily demonstrated that the position of the constricting clamp controlling the rate of fluid flow is of critical importance. For example, consider a single channel set with a single fluid control clamp. If the tubing is punctured above the constricting clamp fluid leaks out. In contrast, if the puncture is below the constricting clamp large quantities of air may enter the tubing and travel to the vein.

The constricting clamp controlling flow should, therefore, be as close to the vein used for injection as possible. The fluid administration set should be tested for leaks prior to use.

The above discussion, admittedly incomplete, is intended to awaken interest (and vigilance) in air embolism as a significant hazard of fluid therapy. Additional information can be found in reviews by Kerr[2] and by Bailey.[1]

Rates of Fluid Administration

"Morphine Sulfate 15 mg. (h) p.r.n." If this order were to appear in the physician's order book of a well-run nursing station, the nurse would probably insist on a statement of how frequently the morphine may be given. Otherwise the order as erroneously written permits a rate of morphine injection of, for example, 15 mg. every five minutes.

"One liter of 10% glucose in isotonic saline i.v." Unfortunately this is the customary form of an order for intravenous fluids and, in this instance, the nurse will probably not insist on a statement of injection rate. Nevertheless under certain circumstances the intravenous injection of fluids at an improper rate may be as catastrophic as overly rapid administration of morphine.

A physician's order for parenteral fluids which fails to specify the desired rate of flow both in drops per minute and in c.c. per hour is written incorrectly. It should be a hospital rule that the fluid prescription includes both of these rate specifications. If these rate factors are omitted, or if they are included but not conscientiously enforced, the rate of fluid administration becomes a guess work affair inviting the serious consequences of too rapid or of too slow infusion. Why most of us consider it the physician's responsibility to decide upon the quantity and composition of intravenous fluid but in effect frequently evade the responsibility of selecting *and enforcing* an appropriate rate is something of a mystery.

It is surprising how often, in attempting to exercise control over rate, the physician assumes that one c.c. of fluid is equivalent to 15 drops. The number of drops in a given volume of fluid injected through an infusion drip chamber is determined primarily by the size of the orifice which delivers the fluid into the chamber. This orifice varies in size depending upon the manufacturer. For example, Abbott sets deliver about 20 drops per c.c. of fluid whereas Baxter sets deliver only 10 drops per c.c. Abbott has recently released a so-called microdrip affair which provides 43 to 45 drops per c.c. (useful for slow rates of flow; for example in babies or children).

The control of flow rate is critically related to the character of the clamp used in constricting the tubing. Many of the disposable sets provided by leading suppliers of parenteral fluids have clamps which require much time and effort to achieve precise adjustment of rate. Such clamps should be replaced by suitable screw or tunnel-type clamps. Nevertheless, not even the most precise clamp is a substitute for eternal vigilance since unless the infusion rate is checked and if necessary adjusted at frequent intervals, rates of flow may undergo striking increase or decrease as a result of change of position of the extremity, change in tone of the vein, or change in location of the needle.

Several types of disaster can be traced to lack of interest in rate control. Thus blood and other fluids given too fast to patients with diseases of the heart or lungs have produced pulmonary edema. Fluid administered too slowly has failed to remedy dehydration and mineral deficits. Glucose and other hexoses injected too rapidly have resulted in self-defeating melituria, osmotic diuresis, and increased urinary loss of electrolyte. Infrequent observation of flow rate has caused "runaways;" this is particularly unforgivable and tragic in infants and children. When one delves into the causes of such errors it may be apparent that the prescribing physician had intended that the fluid be given at a proper rate. In this sense the catastrophe may be regarded as a failure of the physician to translate intention into actuality.

An atmosphere of cooperation and understanding must be cultivated in each hospital in regard to this matter of rate control. Thus nurses, housestaff, attendants, and attending physicians must come to appreciate the importance of enforcing prescribed rates of flow 24 hours per day and seven days per week. Their appreciation of this can come from checks on flow in the course of fluid therapy in a given patient as well as from conversations, lectures, demonstrations, memoranda, and ground rules. Adequate quality and quantity of personnel and facilities are obvious prerequisites. The practical aspects and plans are best analyzed on an individual basis taking into account the peculiarities of the individual hospital.

There are all too few rules of thumb which I can proffer in regard to exactly which flow rate should be selected for a given situation. Among usually recognized factors which must be taken into consideration are: Type and quantity of fluid prescribed; technical matters such as availability of veins; comfort of the patient; continuous preven-

tion of ketosis; status of heart, lungs, and kidneys; rates of glucose utilization. The latter is probably less than 0.5 grams of glucose per kilo of body weight per hour in the starved subject because of "starvation diabetes." In the hydrated, non-starved subject a safe figure is probably about 0.5 grams per kilo per hour or somewhat higher. It is very useful to test the urine for sugar at regular intervals. If glycosuria is less than 3+ it is probably of little importance in causing wastage of water and electrolytes.

Daily Measurement of Accurate Body Weight

How much fluid shall I prescribe for this patient during the next twenty-four hours? This is one of the burning questions each clinician strives to answer satisfactorily as he treats patients with parenteral fluids. A valuable help in answering this question is afforded by knowing whether the water stores of the patient have increased, decreased, or remained unchanged. A simple example is the patient who on day No. 1 is assumed to have a normal quantity of body water, and who 24 hours later is found to have sustained a net loss of body water approximating 2 liters. The crux of the matter is that estimates of change in the quantity of body water are best and most accurately made by serial (usually daily) measurement of body weight.

History, physical examination, chemical and other laboratory data, measurement of intake and output, knowledge of underlying illness—all are highly significant, invaluable contributors to successful fluid therapy. But, useful and crucial though they may be, none holds a candle to the utility of serial body weights in reflecting day-to-day changes in body water. And a bit of reflection should show that knowledge of change in body water is one of the principal determinants of the answer to the question: How much fluid is appropriate for the next 24 hour period?

It can be reasonably assumed, for purposes of fluid therapy, that about 0.1 to 0.4 kilograms of body weight is the range of daily loss in an adult sustained on parenteral fluids provided that no deficiency of body water has developed. The extent of this non-water component of weight change depends upon the balance between caloric intake and caloric need. This balance may vary considerably. But even if the caloric intake is negligible, non-water loss should fall within 0.4 kilograms if adequate fluids are provided. For example, if accurate body weights show that a patient has lost 0.3 kilograms of weight in 24 hours, an insignificant change in body water can be inferred. On the other hand, if the authentic 24 hour weight loss is 2.3 kilograms a decrease in body water of about 2 liters is suggested.

This estimate of change in body water is most readily inferred from change in weight rather than from other information which can be brought to bear on the problem. Thus, consider a patient who on day No. 1 is normally hydrated and weighs 60.0 kg. (Table 1). Assume that this patient is losing fluid from the gastrointestinal tract over the next few days and parenteral fluids are the exclusive source of intake. The daily loss in body weight shown (Table 1) is less than 0.4 kg. Therefore it can be safely assumed that no significant change in the total quantity of body water has occurred. Suppose, however, that the weight were found to be 57.7 kg. instead of 59.7 kg. on day No. 2. This loss of 2.3 kg. would define a deficit of body water of about 2 liters.

Day	Weight (Kg.)
1	60.0
2	59.7
3	59.7
4	59.4

Table 1

How readily can this 24 hour loss of 2 liters of body water be detected by means other than serial measurement of body weight? The clinical history and physical findings during this 24 hour period would at best yield useful qualitative information. Accurate measurement of intake and output is an indispensable component of optimal fluid therapy. Even such measurement, however, does not include variable

loss of water through skin and respiration. Nor are anything resembling accurate measurements of output of fluid usually available to the clinician. Moreover certain types of gastrointestinal losses (among others), for example profuse drainage from a fistula, vomiting, and diarrhea, lend themselves poorly to quantitative collection. Hence measurable intake and output are unworthy substitutes for serial body weights in relation to change in body water. As already emphasized, however, serial body weights do not yield the vital information gleaned from knowledge of intake and output. The latter data are useful in judging the composition of replacement fluids; body weight change sheds no light on this problem.

Laboratory data generally available in hospitals, although crucial for many aspects of fluid therapy, would yield no more than a clue concerning the 2 liter deficit of water. Such measurements would not quantitate the deficit to the extent derived from change in body weight unless direct, ordinarily unavailable, serial measurements of body water were undertaken.

The above reasoning establishes the supremacy of serial measurement of body weight in estimating change in body water and thus in helping to guide the quantity of fluid prescribed. At the same time body weights are not proper substitutes for clinical history, physical examination, laboratory data, and measurements of intake and outgo. These have their own special utility and, although beyond the scope of this presentation, all must be taken into account in devising a proper fluid prescription.

Two major problem appear to conspire against obtaining body weight measurements which are meaningful for fluid therapy: Firstly, the bed fast patient is frequently not weighed because of alleged technical difficulties. This fact is in a sense tantamount to stating that the more serious the illness the less is the need for objective criteria to guide fluid therapy. There is at least one commercially available scale[3] which facilitates weighing of bed fast patients. Secondly, many measurements of body weight are about as useful as no measurements at all. This is true because of the grim fact that body weights as ordinarily measured in hospitals are subject to gross inaccuracy. This then resembles the situation in regard to accurate intake and output data save for the fact that obtaining a precise body weight is intrinsically simpler and less demanding of time and effort.

Weighing a patient with a blanket on one day and without this blanket 24 hours later may be reported as a loss of body weight of 2 kg. or more. This apparent loss of body water could lead to disastrous treatment. Physicians charged with the responsibility of fluid therapy have by this very fact accepted the responsibility for providing a carefully thought-out, continuously supervised program of body weight measurements which meets the needs of their individual hospitals. Even those prescribing fluids for infants and children oftentimes ignore the comparatively simple problem of arranging for accurate body weights and evidently prefer instead a kind of roulette wheel guidance. Is it unreasonable to suggest that an era in which gargantuan feats in the operating room are almost commonplace should also be characterized by the ease with which accurate body weights can be obtained and interpreted?

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DISCUSSION

DOCTOR DuVAL: Doctor Tarail, would you restate the situation with respect to the drops per minute. It may have been implied this morning that the number of drops per minute varies with the tonicity and specific density of the solution. Although this is actually true, from a practical clinical viewpoint, I think you were probably referring more to the size of the nipple of the equipment itself. Would you like to restate that?

DOCTOR TARAIL: Yes. Doctor DuVal hit the nail on the head. It makes very little difference from the practical point of view what the specific gravity of the solution being administered is. Even blood, which has higher specific gravity, of course, than most solutions, can be used with the figures that I gave you. The size of the drop is determined by the characteristics of the equipment. With Baxter sets, irrespective of the type of fluid being administered,

one can, in round numbers, say that ten drops is equivalent to one milliliter of fluid; and with the Abbott set, with its size of opening, one has to allow for twenty drops per cc. of administered fluid. The specific gravity is then a relatively minor, and from a practical point of view, insignificant part of this problem.

DOCTOR DuVAL: In what position should a patient be placed, in whom air embolism is suspected, in order to prevent air embolism to the brain; and does the venous pressure of the patient have any bearing on the occurrence of air embolism?

DOCTOR TARAIL: It is generally advised that the head be quite low, below the rest of the body, so that bubbles will not rise to the head and injure the vital structures, but rather go into the vessels lower down. Then the bubbles can be reabsorbed in the course of time, relatively safely. In addition, the patient should be placed on the left side. This is thought to allow for an accumulation of the air in the apex of the right ventricle. Whereas, if the patient is lying flat, there is more tendency for accumulation of the air at the orifice of the pulmonary outlet from the right ventricle. If the bubbles are placed so that they are next to the orifice leading to the lung, then there will be an ineffectual contraction of the ventricle upon the air. The air is compressible, unlike the blood, and nothing will move. To recapitulate, the patient should be on the left side, with the right side up, and the head very low.

In regard to venous pressure, this, of course, is an important matter in the hydrostatics of the situation in the fluid therapy. If, for some reason, one has an infusion going into the jugular vein and the situation is such that during a phase of the respiratory cycle the venous pressure is below atmospheric, this, of course, will enhance any tendency there might be, because of defective equipment or defective use of equipment, for air to enter. Conversely, if a person has a normal or a high venous pressure, this will tend to oppose the inflow of air.

DOCTOR DuVAL: On the subject of formulas, there must be some here who are wondering, in considering the daily weight, do you use any correction factor or do you assume that there is a one-for-one ratio between weight loss and fluid loss?

DOCTOR TARAIL: One can use the figure 0.1 to 0.4 kilograms for body weight loss as the loss that accrues as a result of tissue destruction **sans** water. So that in regard to dehydration, if the loss of weight exceeds 0.4 kilograms, then one begins to pay heed to it. If it's within that range of 0 to 0.4 klios in 24 hours, this is to be considered as a result of tissue destruction, or weighing the patient with stool one day and without the next day.

And, of course, as Doctor Abbott so neatly pointed out in the course of his discourse, the body weight is no substitute for taking all of the information that can be brought to bear on the problem into account and thinking about it in a slow, meticulous, detailed way.

Use of Osmotic Diuretics in Surgery

J. U. SCHLEGEL

THE PHYSIOLOGICAL HANDLING of water by man is governed by some basic rules which should be appreciated before one can evaluate the changes resulting from trauma. This discussion will be limited to the altered handling of water and electrolytes that occurs following trauma in patients with normal kidneys.

It is generally not realized that a normal individual has a limitation in his ability to excrete water, which is directly related to his intake and excretion of solutes. Kerrigan, Talbot, and Crawford[1] have diagramatically expressed the normal range of physiologic tolerance for water (figure 1) based upon the ability of normal individuals to handle a water load under conditions of varied solute intake. A normal individual who receives only dextrose and water for a 24-hour period has a tolerance for water of

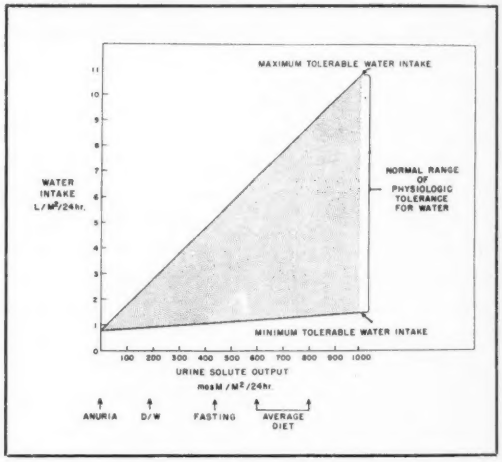

Figure 1. Influence of urine solute output on the body's normal range of physiological tolerance for water (reprinted with permission).[1]

only 3-4 liters (figure 1). A comparable individual on an average or high solute diet has a tolerance for water in the neighborhood of 15-20 liters. This means that an individual with normal regulatory function on a low or no solute intake will dilute his body fluids if he receives fluids in excess of

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Portions of this work have been done by Hans E. Jorgensen, M.D., Fulbright Fellow in Urological Research.

replacement and his physiological tolerance (approximately 2.5 liters per square meter surface area per 24 hours).

Before discussing how such a situation is changed when trauma is imposed, it might be useful to review briefly the present-day concept of kidney function which pertains to the relationship between the physiologic tolerance for water and urine-solute output.[2] In the normal individual an approximate 130 cc. of ultrafiltrate is formed every minute. From this is extracted a variable but large amount in the proximal portion of the nephron, the water supposedly being reabsorbed secondary to the active reabsorption of sodium. Apparently, no concentration nor dilution mechanism is to be found in the proximal tubule, so that the fluid left over from the proximal reabsorption is delivered to the distal tubule and collecting tubules where the change from isotonicity with serum takes place. The amount of nonreabsorbed solutes in the proximal tubule urine determines the amount of water delivered to the distal tubules for final work in regard to dilution or concentration. If sodium reabsorption is high and urea concentration low, as the case would be in an individual on a low solute intake, then the amount of water reabsorbed passively in the proximal tubule would be high, and the amount delivered to the distal tubule would be low. Concentration or dilution of such tubular urine would in a sense be below capacity for the system.

The concentration mechanism, that is, the reabsorption of osmotically-free water, is limited by a maximal capacity ($T^c_{m_{H_2O}}$ approximately 5 cc/min.) which is usually not reached before urine volume exceeds 5-7 cc. per minute. If the load of iso-osmotic urine delivered to the distal tubule is less than $T^c_{m_{H_2O}}$ water reabsorption is limited by the urine to plasma osmotic pressure ratio $\left(\frac{\text{Uosm}}{\text{Posm}}\right)$ which in man is about 4. Maximum utilization of the dilution and concentration mechanisms in the kidney can apparently be ascertained only when enough volume is delivered from the proximal segments of the nephron. Therefore, one way to increase the fluid volume reaching the distal tubule system would be to increase the amount of nonreabsorbed solutes in the proximal tubular urine. This, in essence, is what might be termed an osmotic diuresis and can be obtained by increasing the solute intake which, in a normal individual, could be in the form of an increased protein and/or salt intake. Under ordinary circumstances, 90 per cent of protein digested will be excreted in the form of urea. Consequently, an increase in the protein intake does constitute an increase in the solute intake leading to a higher solute excretion in the form of urea, whereby an osmotic diuresis ensues, resulting in an increase in the physiologic tolerance for water (figure 1).

The excretion of solutes on the operative day, according to Hayes and co-workers,[3] amounts to 205±60 milliosmols per square meter per 24 hours. This figure appears to be in close agreement with figures we have obtained in our studies. Such a low excretion of solutes, resulting from a low intake of solutes, decreases the tolerance for water. A much more severe restriction in the tolerance for water, however, is imposed by the almost obligatory antidiuresis which results from trauma.[3,4,5,6] The actual cause of this antidiuresis of trauma is not known, but it appears to be a result of release of posterior pituitary antidiuretic hormone. Whatever the cause, it is unrelated to serum osmolality and thus cannot be reversed by any attempt to lower the concentration of serum electrolytes. It is sufficient at this point to mention that antidiuresis following trauma in dogs and rats in our experience is at best very short-lasting (hours) and parenterally administered water will not lead to overhydration as the case is in man. It might also be added that in a few cases in the old age group we have observed patients who did not exhibit the usual antidiuretic response to surgery. These had very high pain thresholds, showed little or no apprehension, and in general had remarkable recoveries. Fluid therapy in such patients created no problem, but these are the exception rather than the rule.

The commonly observed post-traumatic antidiuresis usually means that there is no tolerance for water. Returning to figure 1, the water intake in such a patient should be

WEIGHT LOSS AND SOLUTE EXCRETION IN NORMAL CONTROLS DURING 24 HOURS OF INTRAVENOUS FLUIDS

Subject	Sex	Weight Loss grams	Solute Excretion milliosm.
P.J.	Male	2090	791
T.P.	Male	1449	661
J.H.	Male	1838	790
M.L.	Female	1000	428
A.Z.	Female	649	445
K.N.	Female	1146	489

Table I

identical with the minimal tolerable water intake. Any excess of water will lead to dilution of serum electrolytes and an expansion of body fluids. To evaluate this, it is essential that a baseline be established regarding weight and serum electrolyte changes in normal individuals on bed-rest, receiving parenteral fluids only. Evaluation of weight and serum electrolyte changes in post-operative patients must be compared with changes occurring in normal unoperated controls treated identically. In Table I are presented some baseline data from six normal individuals, three males and three females. They were on bed-rest and subjected to the routine procedures of no oral intake after midnight and from 9 a.m. the following morning they were given parenteral fluids consisting of dextrose in water. They were weighed before the intravenous fluids were started at 9 a.m., and again 24 hours later. The weight loss in grams and the amount of solutes excreted in the urine, expressed in milliosmols, are presented. All figures are corrected to 1.73 square meter surface area. The females appeared to lose somewhat less than the males. There were no changes in serum electrolytes.

A group of 18 surgical patients who received an approximate 2000 cc. of dextrose in water intravenously during the operative day (24 hours) showed a mean weight loss of 164±226 gm. The serum sodium in these rectly proportional to the excretion of solpatients on the day following surgery showed a decrease of 3.78±0.77 per cent, compared to the preoperative level. These fig-

Table II
PATIENTS RECEIVING 5 PER CENT DEXTROSE INFUSIONS WITH 4 PER CENT UREA.

Subject	Intake H_2O cc.	Urine per cent of intake	Urea excreted per cent of intake	Na balance meq.	Serum Na per cent change	Serum osmolarity (corrected per cent change)	BUN change mg. per cent	Weight change grams
			A. (Appr. 4000 cc. Intake)					
E.C.	4000	102.0	73.6	—126	—2.1	—1.4	+56.3	— 500
H.D.	4000	92.7	54.0	— 97	—2.1	—0.7	+34.7	—1100
C.H.	3845	95.3	69.7	— 29	—0.2	+1.5	+26.3	— 800
G.E.	4210	86.2	56.2	— 24	+2.5	+6.0	+65.5	— 900
R.L.	4004	100.0	72.4	—118	—1.6	—0.3	+41.7	—1350
H.F.	4000	81.5	46.5	+ 55	—0.4	+2.5	+68.9	—1650
A.L.	4000	93.2	71.5	—108	—1.8	—1.1	+48.7	—1750
C.S.	4100	72.1	36.7	— 9	+3.6	+1.0	+61.3	—1400
P.M.	4000	83.1	56.3	— 37	—1.7	+1.4	+60.5	—1150
H.F.	4000	93.8	54.5	+ 29	+4.0	+4.2	+35.3	—1900
Mean	4016	90.0	59.1	—46.4	+0.2	+1.3	+49.9	—1250
			B. (Appr. 3000 cc. Intake)					
C.W.	2750	87.3	57.3	+ 15	+2.4	—1.4	+48.5	— 450
H.H.	2590	93.6	52.4	— 51	—3.2	—1.4	+61.3	— 500
I.L.	3350	103.0	65.1	— 18	—0.3	+2.2	+39.2	—1400
H.W.	3300	87.1	66.2	— 6	—2.6	—6.1	+50.1	— 950
J.A.	3000	77.4	49.6	+ 13	+1.1	+2.1	+44.8	— 550
Mean	2998	89.7	58.1	—9.4	—0.5	—0.9	+48.8	— 770

ures, when compared with the normal controls, must indicate that all these patients have actually been overhydrated, their weight loss was less than that of the normal controls, and their serum sodium diluted.

To create an osmotic diuresis under such circumstances will not increase the water tolerance. However, it is well known that during antidiuresis the urine volume is dilute. We have shown that administration of 4 per cent urea intravenously given with dextrose and water will increase the volume output and that large amounts of intravenous fluids can be given in this fashion without any danger of overhydration.[6,7,8] Table 2 presents the data from two groups of patients subjected to suprapubic prostatectomies, who received 4 and 3 liters respectively of intravenous infusions containing 4 per cent urea. It will be noticed that the weight changes are rather close to those of the normal controls and there are practically no changes in either serum sodium or serum osmolarity.

In short, one might say that following trauma, the normal range of physiological tolerance for water does not exist. In fact, there is no range. The tolerance for water is nil, so only replacement can be given without running the risk of overhydration. In utilizing osmotic diuresis, one does not increase the tolerance for water but replaces water with a solution containing a solute that can be excreted by the kidney under the conditions of antidiuresis, meaning that the concentration of the solute given must be of approximately the same concentration as it is in the urine excreted. If one were to give higher concentrations than 4 per cent urea, dehydration would result. Dehydration could likewise result if large amounts of 4 per cent urea were given intravenously. However, this would rarely have practical significance since one would have to exceed 8 to 9 liters a day. ($T^c_{H_2O}$ does not become constant before urine volume exceeds 5 to 7 cc/min.)[2]

To summarize the question of tolerance for fluid on the day of surgery or the day of trauma, one might state that water cannot be tolerated in excess of replacement. However, water with a solute in suitable concentration, such as 4 per cent urea, can be given in any desired quantity with a maximum of an approximate 8 to 9 liters per 24 hours. We have thus not changed the lack of tolerance for water, but we still have tolerance for fluids such as 4 per cent urea, which can be utilized if a high urinary volume is desired. It might further be added that urea administration in amount and concentrations as used here does not change sodium excretion.[8]

Before discussing the situations where high urinary volume may be desirable or perhaps even imperative, it may be worthwhile to point out that use of osmotic diuresis in surgery has been made in this department, in a study on sodium retention following trauma.[9] It has been suggested that a lowered serum sodium level leads to retention of sodium, probably through an increased production of aldosterone. Since dilution of serum sodium occurs following most cases of trauma where severe restriction of water has not been emphasized, it was found useful to evaluate the sodium retention in patients given 4 per cent urea intravenously rather than dextrose in water, alone. In the previously mentioned 18 surgical patients who were given approximately 2000 cc. of dextrose in water, the serum sodium showed a drop amounting to 3.78 ± 0.77 per cent of the preoperative level. In 30 surgical patients, 4 per cent urea was given with dextrose in water, leading to weight losses more comparable to our control group of non-operated individuals (1164 ± 173 gm.) and no drop in serum sodium (-0.18 ± 0.62 per cent). This latter group, however, showed sodium retention, which must have been unrelated to serum sodium levels. This is inserted just to point out the value of the use of osmotic diuresis in surgery for the study of physiological phenomena associated with trauma.

Are there any situations in which the use of an osmotic diuresis in surgery is of real practical significance? The answer to this, I believe, is that there are situations in which a high urinary volume is to be desired and, at times perhaps, even essential. At other times, it probably is non-essential but practical.

It appears reasonable that, in any situation where nephrotoxic substances might be present, a dilution of such substances by promoting an osmotic diuresis could be beneficial. It has, for instance, been shown that the combination of hemoglobinemia, renal ischemia, and antidiuresis is dogs could result in renal damage, where none of the individual factors alone would result in such.[10] However, this damage was prevented when osmotic diuresis was established by the administration of mannitol.

In cases of gross hematuria, as seen for instance following urological surgery, an internal irrigation can be achieved by means of high urinary output feasible only following the trauma by an osmotic diuresis. We have thus given up to 5 liters of fluid with 4 per cent urea intravenously to patients following suprapubic prostatectomies during the first 24 hours of surgery. This is definitely a simplification in the management of these patients, since frequent bladder irrigations are no longer necessary and subsequently the dangers of infection with contaminated irrigation fluid are eliminated.

Crush injuries and thermal injuries constitute special problems since extensive replacement therapy is imperative but often difficult to evaluate accurately. According to Moore[11] a severe burn on the average, in an adult, when adequately treated usually results in a total weight gain approximating somewhere between 8 to 10 per cent of the patient's normal body weight. Hardy and co-workers[12] report weight gains in severely burned adults ranging from 5-12 kilograms. In Table III are presented weight changes in 8 burn cases given only enough saline and blood to maintain blood pressure and pulse rate. The amounts of saline given were in some cases only one-half to two-thirds of those recommended by the Brooke formula.[13] Further fluid therapy consisted of 4 per cent urea in dextrose and water in an amount sufficient to maintain a urine volume between 100-200 cc/hour. The serum sodium concentration was unchanged within the first 24-48 hour period following the burn, showing neither any increase nor any decrease ($+0.46 \pm 1.00$ per cent). The weight increases in these patients are far less than what is considered necessary in the light of formation of obligatory edema. We consequently feel that obligatory edema in burns is not as great as has hitherto been thought and that a closer approximation is reached when an osmotic diuresis is established with 4 per cent urea. It might be added that we feel that this approach to the treatment of burns appears to be a tremendous simplification and certainly completely eliminates the hazards of overhydration.

The use of osmotic diuresis in surgery for the purpose of dehydrating the patient, using concentrations in excess of those that can be handled by the kidney, can be applied in patients where previous overhydration has led to hyponatremia.[14] Dehydration of neuro-surgical patients with urea in concentrations from 5 to 30 per cent has been used with apparent benefit.[15,16]

Having discussed the usefulness and definite place in therapy for solute diuresis, whether it be urea, mannitol, sucrose or even low molecular weight Dextran, one must add

INITIAL WEIGHT GAINS IN BURN CASES GIVEN 4% UREA INTRAVENOUSLY

No.	Patient	Sex	Age	Extent of Burn %	36-48 Hours Weight Change %	Clinical Course
1.	D.R.	Male	3	50-60	+6.0	Died 10th Day
2.	H.S.	Male	37	20	+2.9	Recovered
3.	C.N.	Male	2	50-60	+9.3	Recovered
4.	C.B.	Male	44	40	+5.2	Recovered
5.	M.L.	Female	59	30	+4.6	Died 12th Day
6.	W.W.	Male	40	30	+5.8	Recovered
7.	A.C.	Male	41	60	+3.9	Died 9th Day
8.	T.B.	Female	5	45-50	+5.5	Recovered

Table III

that cases where such therapy is truly indicated actually constitute a minor portion of those seen by the general surgeon. The average surgical patient will have no particular benefit from an osmotic diuresis, but will usually do perfectly well if proper restriction of fluids is observed on the day of surgery as well as the following 2-3 days. Proper restrictions however, according to Hayes, et al.,[3] mean administration of only approximately 1700 cc. dextrose in water per 1.73 square meter surface area on the operative day in excess of possible replacement. We have, however, seen several patients receiving this amount exhibiting weight losses considerably less than those seen in our non-operated controls, and exhibiting dilution of their serum electrolytes. Quite frequently an intravenous drip is maintained, especially in patients where replacement of losses is necessary. If the drip is not maintained at a slow enough rate, overhydration under such circumstances frequently results. If the drip was maintained with a solution containing a solute such as urea in a concentration of 4 per cent, overhydration would be impossible provided the patient is not in shock. We therefore feel that, even in patients where the establishment of an osmotic diuresis is not of particular importance, the use of a solute in the intravenous fluid in a suitable concentration will insure the patient against overhydration and make the parenteral fluid therapy much safer.

In conclusion, it might be said that the use of the osmotic diuresis in surgery is a definite step forward. It has a usefulness, in certain cases, which can be life-saving. In other cases it might just be a safeguard against overhydration. The type of solute used is of little significance as long as it is a substance which will be excreted in the urine, since it otherwise would not act as an osmotic diuretic. We have found urea the most useful agent so far, since it is a physiologically-occurring substance with little or no toxic effect, which will distribute over total body water and thus can be given more safely to persons with impaired cardiovascular function. Mannitol and sucrose have the disadvantage of remaining in the extracellular space, thus by virtue of their osmotic effect causing an expansion of this space, which possibly could constitute a hazard in persons with borderline cardiac function. Urea has the disadvantage of being very heat-labile, requiring sterilization by filtration, and storage either in lyophilized form or under refrigeration. It further has to be given with dextrose or saline since urea in water alone can cause hemolysis. These latter disadvantages are, however, minor and cause no serious problems. We have for the past years used urea-containing solutions on many hundreds of patients and have never encountered any side effects nor difficulties of any sort.

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DISCUSSION

DOCTOR FREED, Assistant Professor of Medicine, University of Oklahoma School of Medicine: Doctor Schlegel, is there a commercial urea available for intravenous use?

DOCTOR SCHLEGEL: Urea is now available in lyophilized form from Abbott Laboratories.

DOCTOR COOKE: May I comment on urea?

DOCTOR FREED: By all means; go right ahead.

DOCTOR COOKE: There is one thing I would like to emphasize, and that is that not all patients can be assumed to have the capacity to concentrate their urine. I think this is particularly pertinent to the problem of the use of urea.

DOCTOR SCHLEGEL:: I would like to state that I did not emphasize that the use of 4 per cent urea was in people with normal kidneys. However, there is a very simple tool whereby this can be evaluated, and that is to do an osmotic pressure determination on the urine or just evaluate the response. There is one thing I think should be said in regard to giving urea. It is very difficult, if not impossible, to pull out any excess sodium that you have given. If you pull out too much water, however, such can be readily given back again.

The Problem of Water Intoxication in Pediatrics and Surgery

ROBERT E. COOKE

WATER INTOXICATION may be defined as the complex of neurologic symptoms resulting from a rapid decrease in the osmolarity of extracellular fluid. Since sodium chloride represents the bulk solute of extracellular fluid, water intoxication for all practical purposes results from a rapid fall in sodium concentration. Although much has been learned of the causes of hyponatremia, relatively little is known of the mechanisms whereby low sodium concentration leads to neurologic symptoms. Yannet and Darrow[1] demonstrated in cats that lowering of extracellular sodium concentration by peritoneal dialysis without change in total body water resulted in a shift of water from the extracellular to the intracellular compartment. The shift of water in liver and muscle was proportional to the fall in extracellular sodium concentration. By contrast no correlation existed between total water or intracellular water of brain and serum sodium concentration.[2] However, the potassium content of brain fell in proportion to the fall in sodium concentration. A decrease in serum sodium concentration of 1 mEq. per liter was accompanied by a fall in intracellular potassium concentration of approximately 1 mEq. per liter. No information was obtained as to the change in intracellular anions.

However, the neurologic symptoms associated with acute hyponatremia can not be explained on a basis of shifts in brain cell potassium. Utilizing the same experimental techniques Swinyard et al[3] noted a marked reduction of the threshold for seizures induced by electroshock or Metrazol® in hyponatremic rats. This effect could also be obtained without peritoneal dialysis by the administration of large water loads. Convulsions occurred spontaneously in animals subjected to both peritoneal dialysis and water loading. The increased sensitivity to epileptogenic stimuli was maximal 4 hours after paracentesis, could be reversed within 30 minutes by the administration of hy- water was accompanied by a decrease in threshold and vice versa. This finding though considered statistically insignificant is consistent with Rowntree's[5] original observation that cerebrospinal fluid pressure was increased and cerebral edema present at post mortem examination. Nevertheless, in experimental studies the only significant correlation was between electroshock threshold and the concentration of sodium and chloride in serum. Expansion of the extracellular space with isotonic saline produced no change in threshold. Hypernatremia produced gradually by 96 hours of thirsting or ingestion of 5% saline did not elevate threshold. A small quantity of sodium chloride given as a 20% solution intravenously produced a 20% rise in threshold within 30 minutes. These experimental findings are consistent with clinical observations that severe hyponatremia may exist without neurologic disturbance if the changes in extracellular osmolarity occur gradually. Likewise signs and symptoms characteristic of water intoxication have been observed during recovery from hypernatremia even though the serum sodium concentration is still above normal values. Thus the appearance of symptoms seem more closely associated with rate of change of serum sodium concentration than absolute serum levels.

Mechanisms of Hyponatremia

A lowered concentration of sodium in the serum may result (1) from a decrease in the amount of sodium in the extracellular space (2) from an increase in the volume of extracellular water and (3) from a combination of the above two factors (Table 1). Hyponatremia does not usually develop rapidly enough in many of these conditions to be associated with actue neurologic symptons. However, if an additional large water load were given in any of these conditions symptoms might result.

I. Deficiency of Extracellular sodium
- A. Inadequate intake
  1. Low salt diet
  2. Parenteral therapy with glucose in water
- B. Excessive losses
  1. Gastrointestinal—vomiting, salivary, gastric, biliary, pancreatic drainage, diarrhea, resin therapy, enemas (especially megacolon)
  2. Genitourinary
     a. Intrinsic renal disease—chronic nephritis, acute tubular necrosis (recovery phase), nephrosis (diuresis).
     b. Extrinsic influences—mercurial diuretics, diamox®, hypoadrenalism.
     c. Arachnoid—ureterostomy.
  3. Skin
     a. Normal sweat
     b. Abnormal sweat — cystic fibrosis, adrenal insufficiency
  4. Parenteral—thoracentesis, paracentesis, burns
- C. Redistribution
  1. Potassium deficiency
  2. Trauma

II. Expansion of extracellular volume
- A. Excessive intake
  1. Parenteral fluid therapy — glucose in water
  2. Oral (with diminished output)
- B. Diminish output (usual intake)
  1. Renal
     a. Intrinsic—nephritis, nephrosis, tubular necrosis, prematurity.
     b. Extrinsic: (1) excess of antidiuretic hormone—acute central nervous system disease, pitressin therapy, surgery; (2) circulatory—heart failure, cardiovascular surgery, malnutrition.
  2. Skin—premature in high humidity

III. Expansion of extracellular volume and deficiency of extracellular sodium
- A. Excessive losses of sodium associated with retention of water, central nervous system disease, pulmonary disease, pitressin therapy, excessive water therapy.

Table I

pertonic saline and subsided spontaneously within 24 hours. Electrolyte analyses 4 hours after paracentesis revealed a much smaller change in intracellular potassium of brain than was noted at 24 hours.[4] Brain potassium also rose after administration of hypertonic saline. A slight increase in brain

Sodium Depletion

Water intoxication has been observed in infants who were maintained on a very low sodium chloride intake (Lonalac®) because of congenital heart disease. However, most infants may remain on such a regimen for months without developing hyponatremia. Of particular interest and importance in Pediatrics and Surgery a few years ago was the rather frequent occurrence of neurologic symptoms precipitated by the acute loss of sodium from the plasma into water introduced into the colon for therapy or diagnosis of megacolon.[6] Although gelatin in isotonic saline has been recommended for such enemas potassium deficiency may occur on this regimen. Such untoward effects are now avoided by the use of gelatin solutions made up in Darrow's K lacate solution. Salt losing nephritis is occasionally observed in children and acute hyponatremia may develop. The neurologic symptoms resulting from disturbances in osmolarity may be obscured by symptoms of uremia. In hypoadrenalism water intoxication is seen rarely and hyperpotassemia is usually a more important problem. Water intoxication has been observed in such patients after a water load which is not excreted well in the absence of glucocorticoids. Heat stress may also be a precipitating factor because of the high concentration of sodium in the sweat. Arachnoid-ureterostomy for hydrocephalus may be complicated postoperatively by water intoxication because of the loss of cerebrospinal fluid into the urine.[7] At least 35 mEq. (approximately 2.0 grams) of sodium chloride must be added to the usual diet to prevent sodium depletion in such patients. The excessive losses of salt in sweat of patients with cystic fibrosis of the pancreas are rarely associated with symptoms of water intoxication since there is no defect in water excretion and salt depletion develops slowly. Occasionally rapid removal of ascitic fluid followed by excessive thirst and ingestion of water precipitates acute neurologic symptoms.

Expansion of Extracellular Space

More commonly water intoxication results from excessive retention of water rather than loss of salt. A large positive balance

of water may result from excessive intake in the presence of normal or reduced excretion or diminished excretion in the presence of usual intake. Most of the cases observed by the author have been precipitated by excessive administration of glucose in water parenterally.[8,9] Nevertheless, symptoms would probably not have occurred if the usual water diuresis had resulted. Case 1 is an example of iatrogenic water intoxication precipitated by the postoperative administration of volumes of 5 per cent glucose in water possibly appropriate for an adult but not for a child of 4 years.

Case 1. T.C.

A 4 year old white boy weighing 13 Kg. was operated upon at the Johns Hopkins Hospital because of progressive exercise intolerance and increasing cyanosis. A right subclavian to pulmonary artery end to end anastomosis was performed for the correction of a Tetrology of Fallot. The surgical procedure was well tolerated. Only 180 ml. of Dextrose in glucose was given during the operation. After operation 800 ml. of 5% glucose in water was administered intravenously over a period of 12 hours and approximately 140 ml. of water was ingested. This intake was in excess of 360 ml. per 100 calories metabolized. Morphine .2 mg. was administered once during that period. Voiding was observed only once, 12 hours postoperatively. At this time a generalized tonic and clonic convulsion occurred, followed by unresponsiveness. Serum sodium concentration was found to be 117 mEq. per liter. Administration of 300 ml. of isotonic saline over 10 hours led to cessation of seizures and gradual clearing of the sensorium. No central nervous system residuals were observed.

A similar situation may occur when oral rather than parenteral fluids are given if a disturbance in the thirst mechanism as well as the excretory mechanism is present. Case 2 illustrates the dangers which may arise when ad libitum clear liquids are permitted in the early postoperative period or in disorders such as meningitis. In some of these patients significant lowering of extracellular osmolarity fails to inhibit thirst or anti-diuresis as would be expected from Verney's classic studies.[10] Likewise the finding of expanded body water rather than reduced volume makes it unlikely that the volume receptors suggested by Leaf et al[11] are activated and responsible for neurohypophyseal stimulation.

Case 2. L.J.*

A 6 year old white female weighing 16 Kg. was operated upon for ligation of patent ductus arteriosus. Two days before surgery serum analyses revealed normal electrolyte concentrations. Nembutal, morphine and scopolamine were given as preanesthetic medication. Nitrous oxide and cyclopropane-oxygen ether were given over a 3½ hour period. During operation and for the next 18 hours 810 ml. of electrolyte free fluid was given. In addition she ingested in excess of 500 ml. of water and gingerale. This intake was in excess of 240 ml. per 100 calories metabolized. Morphine sulfate was given 4 hours after surgery. Voiding was observed only once in the 18 hours postoperatively. At this time a series of generalized tonic and clonic convulsions occurred. A few hours later the serum sodium concentration was 118 mEq. per liter. Although barbiturates had been without effect, 140 ml. of 3 per cent saline given over 3 hours led to immediate cessation of the seizures and rapid clearing of the sensorium. No residuals were observed.

Since water retention represents an imbalance between intake and output a brief analysis of the quantitative aspects of water excretion is required. The loss of water from the lungs and skin in the absence of sweating is dependent upon a number of variables such as environmental temperature and humidity, rate and depth of respiration, skin temperature etc. By simultaneous measurement of caloric production and insensible water loss it has been shown that evaporative water losses bear a more consistent relationship to caloric production than to surface area particularly in states of disease. Urinary water loss depends upon two factors: (1) the quantity and to a lesser extent the kind of solute presented for excretion; (2) the concentrating activities of the kidney at that moment. The quantity of solute excreted in the fasting state is determined by the rate of turnover of body tissues and bears a closer relationship to heat production than to surface area. For these reasons water loss and water requirements are expressed in terms of units of caloric turnover (per 100 calories metabolized) rather than square meters of body surface.

Insensible water loss amounts to about 45 ml. per 100 calories metabolized and the slight sweating that frequently occurs in a

*This Case as well as Case 3 have been reported previously.[8,9] Over 10 similar cases have been observed in the past 3 years, but in many quantitative data on intake and output are not available.

hospitalized patient in bed raises the usual evaporative losses to 55 to 60 ml. per 100 calories metabolized. Stool losses are normally only 5 to 10 ml. per 100 calories metabolized. The quantity of non-electrolyte solute in the urine during restricted food intake ranges from 10 to 15 mOs per 100 calories metabolized. Urinary concentration in infants and children ranges from just below 100 to slightly above 1000 mOs per liter.

It is possible then to calculate that if water without usually excretable solute (5% glucose in water) is administered in excess of 160 to 200 ml. per 100 calories metabolized excessive retention must occur even in the presence of excellent renal function. In case 1 intake exceeded MAXIMAL excretory capacity by 200 ml. per 100 calories metabolized. Such a rate of administration in 24 hours would lead to a 13 per cent increase in body water and a fall in serum sodium concentration of 17 mEq. per liter. In the presence of some antidiuresis the fall in sodium concentration would be even more precipitous.

As indicated in Case 3 excessive retention of water may occur even when usual amounts of water and electrolytes are administered.

Case 3. D.B.

A 17 months old white boy was admitted because of H. influenzae type b. meningitis. Chloramphenicol, streptomycin, and Gantrisin® were administered. Water, sodium and potassium were given parenterally in amounts not in excess of the usual requirements of the average patient. Approximately 120 ml. of water and 3 mEq. each of sodium and potassium per 100 calories metabolized were administered. The intake amounted to 72 ml. per M^2 per hour. Twelve hours after admission restlessness followed by intermittent grand mal convulsions occurred. The serum sodium concentration was 121 mEq. per liter. Administration of 140 ml. of 3% saline and 100 ml. of whole blood led to prompt cessation of seizures and irritability. Recovery was progressive thereafter.

Water intoxication in surgery and pediatrics results more frequently from diminished renal excretion due to extrinsic influences acting on the kidney rather than to intrinsic renal disease. Although few measurements of anti-diuretic hormone (A.D.H.) levels in the urine or plasma have been made in patients with central nervous system infection or postoperatively, oliguria with relatively high urinary specific gravity has frequently been observed in the presence of adequate water intake. Factors such as massive stimulation of peripheral sensory receptors, circulatory readjustments, morphine or anaesthesia probably stimulate neurohypophyseal release of A.D.H.[12]

The quantitative aspects of the problem can best be appreciated by an hypothetical example. If A.D.H. release is sufficient to lead to a urine osmolarity of 1000 mOs per liter and if the usual renal solute load of 20 mOs per 100 calories metabolized is present (10 mOs non-electrolyte, 10 mOs electrolyte), an intake of water in excess of 80 ml. per 100 calories metabolized will lead to water retention in the absence of increased extrarenal losses. If the usual intake of 1200 ml. per 100 calories metabolized is given, the serum sodium concentration of a 10 kilogram child will be lowered approximately 15 mEq. per liter within two days.

In this discussion of renal solute no distinction has been made between electrolytes and non-electrolytes. Evidence is available that electrolytes obligate more water for excretion than non-electrolytes.[13] The quantitative aspects of this problem have not yet been worked out over a sufficiently wide range of concentrations to permit discussion.

Expansion of Extracellular Space and Sodium Loss

Retention of water leading to expansion of body water may increase sodium excretion markedly. Strauss et al[14] and Leaf et al[15] have demonstrated that sodium excretion may increase rapidly when extracellular volume is expanded even with fluid of low sodium concentration. Some increase in glomerular filtration rate may be responsible but it is also likely that aldosterone release is diminished by the increase in ex-

tracellular volume. Water intoxication has been observed when these phenomena occur rapidly as illustrated in Case 4.

Case 4. A.M.

An 8 year old white boy was admitted to the Grace New Haven Community Hospital because of growth arrest, polyuria and precocious puberty. Diagnostic studies and craniotomy demonstrated a pinealoma which could not be completely removed. Over a period of several months he had recurrent episodes of generalized tonic and clonic convulsions. Serum sodium concentrations at these times ranged from 105 to 120 mEq. per liter. The seizures responded promptly each time, except terminally, to the administration of small amounts of 3 per cent saline. Balance studies were attempted on several occasions. Although some losses were incurred because of lack of cooperation, a consistent pattern of metabolic response was observed as illustrated in Table 2. Administration of pitressin led to reduction in urine volume and water intake. A small positive balance of water with a gain in body weight of 1 to 2 per cent occurred. Serum sodium concentration which was uniformly high prior to pitressin therapy fell precipitously. Urinary sodium excretion which was low when urine volume and serum sodium level were high rose markedly and was quantitatively responsible for the sharp fall in serum sodium concentration and symptoms of water intoxication.

Abnormal regulation of thirst must be present in such cases of central nervous system disease. In addition the mechanism responsible for loss of sodium seems unduly sensitive to relatively slight expansion of body water. Repeated measurements of sodium excretion indicate that when urinary water loss is high and body weight low urinary sodium excretion is low and serum sodium concentration high. When water output is low (pitressin therapy) and body weight increases by 1 or 2 per cent urinary sodium excretion rises markedly and serum sodium concentration falls to very low levels. Symptoms of water intoxication appear sporadically and seem to bear a closer relationship to the rapidity of change in sodium concentration than the absolute level.

Treatment

The emergency treatment of water intoxication is similar regardless of the mechanisms leading to hyponatremia. The usual anticonvulsants are ineffective in treating the seizures of water intoxication. Hypertonic saline should be given intravenously in amounts* adequate to raise the sodium concentration about 5 mEq. per liter in two hours. Since hypopotassemia is associated in some patients with hyponatremia and since symptoms and signs of potassium deficiency (especially cardiac) may be increased by elevation of the sodium concentration potassium should be added when pretreatment serum potassium levels are normal or low. Some cases of hyponatremia are associated with severe hyperpotassemia[9] and caution must be exercised.

The subsequent therapy of the patient must be individualized. When volume is expanded limitation of water intake or use of alcohol to invoke a water diuresis is indicated. When sodium depletion is present salt intake must be increased.

Conclusion

Since severe brain damage may occasionally remain as a residual of water intoxica-

* $\frac{(Cd - Ca) \times fd \times B.W}{(\text{Concentration desired} - \text{C. actual}) \times \text{distribution factor} \times \text{body weight}} = \text{mEq. of Na}$

$5 \times 0.6 \times B\ Wt \times 2 = \text{ml. of } 3\%\ NaCl.$

Sample Time	Metabolic Data Case 4 A.M.						
	Average Intake		Average Output		Body Weight	Serum Na	Remarks
	H_2O g per day	Na mEq per day	H_2O g per day	Na mEq per day	Kg	mEq/l	
11/23	600	35	300	29	15.5	146	Pitressin 0.4 ml b.i.d.
11/25	800	35	640	120	15.7	141	"
11/29	700	35	400	136	15.9	120	Convulsions
12/16	4500	35	4900	15	15.5	132	

Table 2

tion, prevention of this disorder is essential. As indicated in earlier discussions prevention depends upon the supply of adequate electrolyte to meet abnormal losses and limitation of water intake so that excessive retention does not occur. Total metabolism of the body varies considerably for a given body weight or surface area in pathological states such as fever, hypothermia, endocrinopathies. Since the turnover of body water and electrolyte is related to total metabolism, maintenance requirements for these materials, just as for protein and calories, should be calculated in terms of this parameter rather than surface area or body weight. Even with such a system of calculating therapy severe derangements in body composition will occur unless disturbances in the usual homeostatic mechanisms are suspected in specific clinical states.

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Central Nervous System Factors in Water and Electrolyte Metabolism

JOHN H. BLAND

PRIMARY METABOLIC DISORDERS may exert strong influences on central nervous system function; and certain structures within the central nervous system may produce profound metabolic effects. Disease and trauma of the brain has been associated with abnormal water and sodium metabolism; potassium depletion; azotemia and acidosis.

It is generally accepted that oliguria and retention of sodium accompany nearly all serious illness or trauma, related or unrelated to the central nervous system. There is much evidence to suggest that the stimuli producing salt and water retention are mediated via the central nervous system to the hypothalamus; then a neuro-endocrine stimulus reaches endocrine glands which secrete hormones regulating renal excretion of water and sodium.

This discussion will be confined to two areas:

(A) The central nervous system factors, known and postulated, normally regulating water and sodium metabolism.

(B) Hyperosmolar syndrome of central nervous system disease and its relationship to the normal reaction to dehydration.

PART I

Relationship of Hypothalamus, Posterior Pituitary Gland, Anti-Diuretic Hormone and Water

Antidiuretic hormone of the posterior pituitary gland is the principal agent regulating water excretion. Its action is on the distal tubule of the kidney. It promotes reabsorption of the solute free water.* Through the sustained efforts of du Vigneaud and his associates[1,2] the two hormones, Pitressin (ADH) and Pitocin (Oxy-

*Urine volume may be divided into two parts, osmolar water and solute free water. Osmolar water is that part necessary to contain urine solutes in a solution isoosmotic with plasma; solute free water is the remaining urine volume. Solute free water is reabsorbed from the distal tubule with ADH action; it is retained in the excreted urine during water diuresis (ADH suppression).

tocin) were purified and recently synthesized. They are both polypeptides containing eight amino acids per molecule. Six amino acids in the two hormones are identical; two are different.

It is unsettled whether these hormones are separately secreted or represent fragments of a single large protein molecule originally possessing activities of both. The fact that antidiuretic properties have been noted in plasma proteins,[4] might be construed as evidence for secretion of large molecular proteins from the pituitary gland. Small polypeptides, however, may be released and subsequently bound to plasma proteins as transport mechanism.

The current concept regarding posterior pituitary hormones is that they are secreted by the neurones of the supraoptic and paraventricular nuclei; then transported distally along the axones to the posterior lobe for storage in nerve endings close to blood vessels in this area.[4] The posterior lobe probably serves as a reservoir of manufactured hormone available for instant release into the systemic circulation as needs arise. This concept was a giant step in endocrinology and directs attention to the hypothalamus as the structure governing water metabolism through the pituitary body.

Verney[3] clearly established regulation of water excretion by an osmoreceptor located in the distribution of the internal carotid artery. The osmoreceptor is sensitive to osmotic pressure changes in the plasma. It modifies rate of ADH release in accordance with state of hydration. With increase in osmotic pressure, hyperosmolarity, and consequent movement of water from cells (cellular dehydration) antidiuretic hormone is released. With fall in osmotic pressure (hypoosmolarity) ADH release is suppressed.

Precise location of the osmoreceptors is not established. There is some evidence that they exist in the supraoptic nuclei in an intracellular position.[29] Dingman,[4] suggests that the osmoreceptor site may be in the posterior lobe. This is based on observations in patients who have had hypophysectomy as therapy of carcinoma. In such patients osmoreceptor control of available ADH was apparently lost or much diminished. The osmoreceptor response to hypertonic saline is absent more frequently than present—or else not as prompt and sustained. Osmoreceptor activity may depend on the saving of a part of the posterior lobe or pituritary stalk.

Another somewhat obscure pathway to the posterior pituitary involves a "volume receptor." A volume receptor promoting both sodium and water retention has been located somewhere in the head portion of the vascular tree. It is stimulated by a decreased circulating or effective blood volume; it is suppressed by expansion of blood volume. Prompt secretion of ADH in response to hemorrhage has been observed.[30] This suggests an important role of the posterior pituitary and ADH in regulating volume as well as concentration. Retention of water by volume receptor stimulation by hemorrhage may be sometimes inhibited by previous alcohol administration.[31] This maneuver, however, does not block the retention of sodium. This suggests, at least, that sodium retention may not be mediated directly through ADH via volume receptor stimulus. Presumably a decline in blood volume constitutes a stimulus to aldosterone release, resulting in marked renal sodium retention; an expansion of blood volume suppresses aldosterone release with consequent sodium diuresis.

Oxytocin is also released in large amounts on posterior pituitary stimulation. It has definite effects on sodium excretion.[5] Though the posterior pituitary is not presently implicated strongly in sodium retention this may prove to be the case as more knowledge accumulates regarding the relationships between the two hormones.

Some anti-hypertensive drugs produce water retention, presumably because of their influence on renal circulation or autonomic outflow. However, some of these drugs have potent effects on the mid-brain. They may thus facilitate water retention by stimulating ADH release. This has recently been claimed for hexamethonium.[6]

ADH release is familiarly produced by emotional, physical and physiologic stimuli

and by numerous drugs, e.g., morphine, acetylcholine, nicotine and barbiturates. Dingman[4] et al. have shown that adrenocortical hormones may influence ADH release in man.

Many seemingly divergent factors influence ADH release through hypothalamic mechanisms. It would also seem that stimuli may arise through a variety of avenues, e.g., osmoreceptor, volume receptor, possible alteration of vascular supply of hypothalamic nuclei, direct stimulation of nuclei by drugs or hormones. Nervous impulses may affect nuclei directly; volume impulses influence hypothalamic and posterior pituitary circulation; osmoreceptor stimuli may possibly be confined to the posterior lobe but other stimuli are mediated through hypothalamic nuclei to the posterior pituitary gland.

Dingman[4] formulates that the hypothalamus may be in the position of monitoring stimuli, permitting those of greater intensity or biologic necessity to dominate posterior pituitary activity.

Three major mechanisms of promoting ADH release in order of priority seem to be:[4]

(1) Neurogenic stimulation

(2) Osmoregulation

(3) Volume regulation.

All three may act in combination. It seems probable that inhibitory impulses suppressing ADH release are effective only when stimuli promoting release are quiescent or absent. Volume contraction or neurogenic stimuli promote ADH release in the presence of hypotonicity (a suppressant stimulus) suggesting that they are in higher priority or a stronger stimulus. Nervous impulses take precedence over inhibitory effect of an expanded volume. Hypertonic contraction of blood volume is a much more potent antidiuretic stimulus than is hypertonicity alone; still hypertonic expansion of blood volume if acutely induced evokes ADH discharge. This suggests precedence for osmotic stimulating impulses over inhibitory increased volume impulses. This order of priority is as expected if the primary function of the posterior pituitary and its control of water metabolism is:

(1) Initially to protect and preserve tonicity.

(2) More fundamentally to preserve volume.[4]

Relationship of the Anterior Pituitary Gland, Adrenal Cortex and Sodium Metabolism

The adrenal cortex is the major endocrine structure regulating body content of sodium. Adrenal cortical steroid hormones influencing electrolyte metabolism in man are hydrocortisone, corticosterone (Compound B) and 18 aldocorticosterone (aldosterone). Hydrocortisone and corticosterone are the principal secretory products and have been estimated to be secreted into a ratio of about 12 to 1 normally.[8]

Human adrenal gland has been estimated to secrete 17 to 29 mgs. of hydrocortisone and 2-3 mgs. of corticosterone/day. Beef adrenal gland contains only 45-95 micrograms per kilogram of aldosterone. Only traces are found in normal venous blood or urine. The present exciting investigations regarding aldosterone and its mechanism of secretion may have overshadowed importance of relationships of this hormone with hydrocortisone and corticosterone in understanding sodium metabolism.

Hydrocortisone[32] and corticosterone[33] secretion have been shown to follow a diurnal rhythm, highest in the early morning, falling sharply in the late afternoon and reaching its lowest level during sleep. A similar diurnal rhythm in excretion of aldosterone has not been confirmed.

A diurnal pattern for sodium excretion, mainly resulting from alterations in renal tubular reabsorption follows just behind the adrenal cortical rhythm of hormone secretion by only a few hours;[34] its peak occurs in the forenoon or at noon; its lowest level is during the night; this suggests an interrelationship between rhythmic adrenal secretion and sodium excretion.

Though one thinks of hydrocortisone, corticosterone, meticorten and cortisone as being sodium retaining steroids Ingle and

Thorn[9] and Sweat[10] have shown that very small doses of these steroids promotes loss of soduim by a decreased renal tubular reabsorption. More recently this has been studied with intravenously administered steroids in small doses. A sodium diuresis in normal subjects has been demonstrated. Retention of sodium was associated only with administration of large doses.[2] Administration of intravenous hydrocortisone in a dose of 1 mg. per hour to a patient with Addison's disease over a period of 24 hours increased renal excretion of sodium during the day and blocked sodium retaining effect of a small dose of DCA at night.[2]

These studies with physiologic doses of adrenal steroid hormone suggest that diurnal variation of sodium excretion in normal subjects is related to a rhythmic secretion of hydrocortisone influencing renal tubular reabsorption of sodium. The decline at night in sodium excretion may be related to unopposed effects of potent sodium retaining steroid as well as decrease in secretion of hydrocortisone.

Extracellular water volume influences tubular reabsorption of sodium. Contraction of ECW leads to marked sodium retention presumably by volume receptor stimulation. Expansion of ECW results in sodium diuresis, presumably by volume receptor suppression. Adrenal steroids frequently produce expansion of ECW at expense of ICW volume. Such expansion of ECW could promote sodium diuresis by suppression of volume receptor.

It is possible that a diurnal rhythm in ECW volume parallels secretion of hydrocortisone leading to a sodium diuresis during the day and retention at night. Methods of measuring extracellular water volume are not sufficiently accurate to study this effectively.

Aldosterone has been extensively studied recently. It has 20 to 35 times more sodium retaining power than DCA. Increased amounts of this steroid in blood and urine in edematous states has sparked an intensive investigation of its possible role in edema.

Aldosterone secretion is increased by sodium depletion; by administration of potassium; increased production is stimulated by contracted ECW volume and suppressed by an expanded ECW volume.[35] Factors related to volume seem to have primary importane in the regulation of aldosterone secretion. There is still controversy regarding the relation of the anterior pituitary to the secretion of aldosterone. Secretion continues despite anterior pituitary insufficiency. It increases when salt is restricted in such patients. ACTH does cause increased secretion of aldosterone to some degree in normal man. Recently Farrell[11] and colleagues demonstrated a diencephalic substance regulating this secretion. They showed that highly purified corticotrophins enhance it but commercial ACTH preparations do not. Beck[12] and associates showed aldosterone secretion to be increased in man on growth hormone administration (monkey and human growth hormone).

These studies suggest that trophic hormones of hypothalamic or pituitary origin may regulate production of aldosterone. Its continued secretion apparently is assured in the absence of the pituitary gland by such local factors as volume or concentration of ECW.

Guillemin[36] has described studies on neurohypophyseal polypeptides resembling pitressin. It is postulated that these compounds may stimulate release of ACTH from the anterior lobe. It is suggested that areas of the hypothalamus may control not only ADH secretion but also secretion of electrolyte regulating adrenocortical steroids. Neurohormones of the hypothalamus might govern aldosterone secretion, suggesting a possible role of the hypothalamus in sodium metabolism. Definitive studies of precise hypothalamic mechanisms are too few to permit other than speculation.

PART II

Hyperosmolar Syndrome of Central Nervous System Disease and Trauma and Its Relation to Normal Reaction to Dehydration

This discussion will be prefaced by a brief review of the expected, predictable changes

in the central nervous system and circulation initiated by ordinary, moderate to severe water depletion, uncomplicated by central nervous system disease. When simple dehydration occurs in the patient who also happens to have central nervous system disease or injury, on tends to construct a cause and effect relationship between cerebral lesions and the clinical and metabolic picture. When one is dealing with the same type of metabolic deviations, in the absence of any central nervous system dysfunction, he is unlikely to consider cerebral mechanisms as cause.

Body water depletion occurs most commonly in patients who for any reason do not receive or retain an adequate daily supply of water, e.g., comatose or semi responsive patients, children, patients with upper gastrointestinal obstruction or mentally disturbed patients who refuse fluids. The initial event in primary dehydration is rise in extracellular sodium concentration. There is immediate movement of water from cells disturbing the water deficit between cells and ECW. Reapportionment of the water deficit is mediated by the following mechanisms:

(1) Movement of water from cells in response to increased osmolarity of ECW.

(2) Release of cell potassium to ECW with consequent movement of cell water.

(3) Decrease in osmotically active cell cations—with release of further cell water to support ECW. This is simple dehydration.

If dehydration continues the adjustments are not adequate to prevent onset of the physiologic effect of hypertonicity and dehydration. Little change in the circulation occurs early. With moderate to severe dehydration, cardiac output decreases, circulation time is prolonged and there are slight falls in blood pressure. Circulatory collapse is rare because ECW and plasma volumes are so well maintained at the expense of cell water.

Though circulatory changes are minor, central nervous system manifestations occur with considerable regularity in patients with hypertonicity and dehydration. This is expected since central nervous system cells are involved in the general dehydration and hypertonicity and represent the first tissues to show functional change when metabolic necessities such as oxygen and glucose are not available in required amounts. The consequences of advanced cell dehydration was examined by Winkler et al.[17] in animals infused with hypertonic saline to death; death occurs when the pulse is full and bounding and the circulation is well maintained. The same events probably occur in castaways who drink and retain sea water or in patients deprived of water. Broch[18] in 1948 reported hypertonicity and hypernatremia in hospitalized patients following cerebral vascular accident. They received less than adequate amounts of water. Respiratory failure in this group of patients would be assumed to represent a consequence of the cerebral lesion. It might well be related to progressive dehydration. Since Broch's report there have been a number of papers on the hyperosmolar syndrome of central nervous system disease and trauma.[19, 20, 21, 22, 23, 24, 25, 26, 27] Examination of available case reports discloses no case whose clinical and metabolic features are not explicable in terms of the normal reaction to dehydration and to the physiologic consequences of water deficit. This does not, of course, rule out the possibility of a cause intrinsic to the central nervous system.

There can be said to be four types of hyperosmolarity in patients with central nervous system disease.

(1) Simple dehydration in which water requirements are not unusual but fail to be met adequately because of failure of the patient's attendants to evaluate losses and supply adequate amounts.

(2) Hyperosmolarity secondary to unusual demands for water because of either failure of thirst mechanism or failure of hypothalamic-posterior pituitary system to

control renal tubular reabsorption of water, diabetes insipidus. If the patient is unconscious and cannot exhibit thirst polyuria exceeds polysipsia.

(3) Dehydration secondary to unusual demands for fluids because of an especially high solute load presented to the kidney. This occurs in the unconscious patient fed by intragastric tube a diet containing relatively greater amounts of protein without a quantity of water sufficient to excrete nitrogen from the diet. This dehydration will be accelerated if the patient is in negative nitrogen balance or if he has some degree of renal insufficiency preventing excretion of urine of maximal specific gravity. Normal renal response to restriction of fluid intake with an increased nitrogen load is to excrete a urine maximally concentrated, containing a large quantity of urea and very little sodium and chloride. A fairly large volume of high specific gravity urine is excreted, serum shows increasing hypernatremia. As this dehydration progresses, there is, of course, contraction of extracellular volume, diminution in renal blood flow, azotemia and ultimate renal acidosis. The intensity of hyperosmolarity is a function of the discrepancy between water intake, solute load and the renal function capacity. If there is impaired renal function this syndrome may develop rapidly, associated with marked azotemia.

It is apparent that the three types of hyperosmolarity thus noted may occur in differing magnitude in the same patient—all may contribute to a given clinical and metabolic picture.

(4) The last type of hyperosmolarity is sometimes thought to be due directly to cerebral lesions. The supposition that specific cerebral lesions may be responsible for hypernatremia has some experimental support. Stevenson et al.[13] ablated the thirst mechanism and produced hypernatremia by experimental production of bilateral lesions in the ventromedian nuclei of the hypothalamus in rats. Lewy and Gassman[14] noted hyperchloremia in cats after unilateral stimulation of the paroptic nuclei of the hypothalamus.

A direct neural connection between the hypothalamus and the kidney has been postulated.[15,28] It was suggested that a neural connection modifies proximal tubular reabsorption of sodium and chloride. The syndrome of "cerebral salt wasting" has been explained by assuming that the defect is caused by diminished proximal tubular reabsorption of sodium and chloride because of interruption of a neural pathway between hypothalamus and kidney. As a consequence sodium, chloride and water are delivered to the distal tubules in excess. This exceeds the distal tubular reabsorptive ceiling and a continual osmotic diuresis proceeds. Ultimate ECW hypoosmolarity occurs. A similar direct neural connection has been suggested to explain the avid reabsorption of sodium in hyperosmolarity associated with cerebral disease.

If a metabolic or neural mechanism leading to hyperosmolarity due directly to brain lesions occurs or exists it is certainly obscure. It is difficult to evaluate case reports of cerebral damage and hypernatremia; balance data may be lacking. Such patients commonly have intragastric tubes placed in the stomach and may be receiving a relative excess of protein. Azotemia has been commonly reported but it is difficult to rule out renal disease. Potassium depletion has also been reported though less frequently.[27]

Many features of the hyperosmolar syndrome of cerebral damage are entirely consistent with severe dehydration. Hypernatremia, hyponatruria, hypokalemia, hyperkaluria, azotemia and acidosis are all characteristic of advanced dehydration, (severe water depletion). In varying degree this is the biochemical picture in hyperosmolarity of cerebral damage. It has been noted that clinical signs of dehydration are not apparent in these cases. However, since water loss is mainly from cells physical signs of dehydration would appear late, after marked extracellular contraction. Central nervous system signs precede signs of dehydration and circulatory failure. This may be masked by brain lesions.

Comatose neurological or neurosurgical patients are very apt to develop severe wat-

er deficit with much less of a sodium deficit. They often do not experience or express thirst. Fever, sweating and hyperpnea are common in such patients. All these accelerate water loss. The magnitude of sweat water loss is easily underestimated. Hyperventilation water loss is difficult to quantitate. Involvement of the medullary respiratory center may cause hyperpnea. Such insidious loss goes unnoticed. Extrarenal water loss may develop rapidly or gradually. Fever may be due to involvement of the hypothalamic thermoregulatory center. Excess sweating may likewise be caused by a lesion involving the thermoregulatory center. Thus, in a sense the metabolic changes may be indirectly caused by central nervous system lesions.

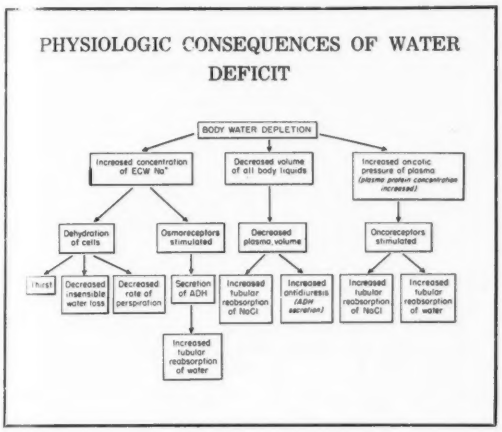
PHYSIOLOGIC CONSEQUENCES OF WATER DEFICIT
BODY WATER DEPLETION
Increased concentration of ECW Na+
Decreased volume of all body liquids
Increased oncotic pressure of plasma (plasma protein concentration increased)
Dehydration of cells
Osmoreceptors stimulated
Decreased plasma volume
Oncoreceptors stimulated
Thirst
Decreased insensible water loss
Decreased rate of perspiration
Secretion of ADH
Increased tubular reabsorption of NaCl
Increased antidiuresis (ADH secretion)
Increased tubular reabsorption of NaCl
Increased tubular reabsorption of water
Increased tubular reabsorption of water

Figure 1

Figure 1 outlines the physiologic consequences of water deficit as outlined and documented in a series of responses formulated in the classic review article by Welt[16] and associates. The first and most important response to water deficit is a rise in sodium concentration of ECW. Immediate transfer of water from cells occurs; ICW compartment repairs the water deficit in ECW. The consequent cellular dehydration constitutes a stimulus to decrease in sweat rate and insensible perspiration. It also initiates thirst sensation.

The hyperosmolarity of ECW results in rise in cellular osmolarity. This stimulates hypothalamic osmoreceptors promoting increased release of antidiuretic hormone from the posterior pituitary increasing renal tubular water reabsorption.

Decline in volume of total body water includes plasma volume contraction. This stimulus promotes increased renal tubular reabsorption of sodium and chloride. It is postulated that this is by the mechanism of a volume receptor, stimulating aldosterone release. This is the most recently documented consequence of water deficit. Striking sodium retention, augmented potassium excretion and ultimate metabolic alkalosis occurs if other forces are not present. Years ago Doctor Peters called this the "reaction to dehydration." Contracted plasma volume is also a further strong stimulus to antidiuresis via the posterior pituitary.

Oncotic pressure of the plasma increases. This likewise is a stimulus to increased tubular reabsorption of both salt and water. Depletion may be augmented by tube feeding of a relatively excessive protein intake. This is especially true following trauma, during the catabolic phase in which the patient is unable to utilize nitrogen. Nitrogen freed in the catabolic phase of the response to trauma plus the urea solute load from the diet places added demands on endogenous sources of water. If dehydration proceeds and plasma volume continues to contract, renal blood flow decreases, oliguria occurs and ultimately, and quite late, peripheral vascular collapse follows.

Thus, a convincing picture can be formulated that the clinical and biochemical features of the hyperosmolar syndrome of cerebral damage may, at least sometimes, constitute an excessive but normal response to extreme water depletion.

It seems that one need not always invoke a cerebral lesion as directly causative of the hyperosmolar syndrome. Severe dehydration can occur readily in the unconscious patient via fever, hyperventilation, sweating, inappropriate amounts of protein in tube feeding and inadequate estimates of water needs. With advanced water depletion it is possible that secondary renal tubular damage may occur due to contracted plasma volume and inadequate renal blood flow. The

hypernatremia, hyponatruria, azotemia, potassium depletion and even acidosis can be explained as a physiologic response to severe water depletion.

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DISCUSSION

DOCTOR FREED: Doctor Bland, can you please outline briefly the best method for treatment of the hyperosmolar syndrome, and does this occur in cerebral vascular accident cases very frequently?

DOCTOR BLAND: The treatment of the hyperosmolar syndrome may vary somewhat, depending on the etiology of its occurrence and the magnitude and duration of extracellular hyperosmolarity, as measured by sodium concentration of serum.

The two main aims in treatment are (a) to provide water as such, (b) to administer as little solute as possible until the hyperosmolarity is well along toward correction.

Water may be given as water by mouth or as a 5 per cent glucose in water by vein. Progress may be gauged by examining serum sodium concentration, urine specific gravity, urine sodium concentration, which is low or absent in advanced hyperosmolar syndromes. Clinical signs observed at the bedside serve as an excellent guide.

A cautionary note should be added. Patients with advanced hyperosmolar syndrome of any cause are usually potassium depleted and in acidosis. Thus the addition of potassium salts as well as sodium bicarbonate may well be indicated.

In regard to frequency of occurrence, I believe it to occur rather more commonly than it is recognized. It occurs frequently in a mild form in many tube-fed patients.

Many such patients, e.g. cerebrovascular accident and head injury, are critically ill. If they are comatose and tube-fed, hyperosmolarity becomes a greater risk. The clinicians tendency wold be to ascribe death in such patients to the cerebral lesion rather than any metabolic cause. I have wondered if some patients in this category dying of respiratory failure might not be dying of hyperosmolarity, potassium depletion and acidosis, respiratory failure being a consequence.

DOCTOR FREED: In the intravenous therapy of an individual with brain injury, are there any dangers in the use of 50 per cent glucose solution, 5 per cent glucose solution, and 10 per cent glucose solution?

DOCTOR BLAND: Yes, I think there is potential danger in using any of those three solutions in a patient with head injury. It has been shown that changes in osmolarity of extracellular fluid, e.g. plasma, is followed promptly by change in hydrostatic pressure of cerebrospinal fluid.[1] With an increase in plasma solute concentration, there is a decrease in cerebrospinal fluid pressure; with decrease in concentration of plasma solutes, there is an increase in cerebrospinal fluid pressure.

In the case of 50 per cent glucose given intravenously, there is an initial sharp rise in glucose concentration and a fall in cerebrospinal fluid pressure due to movement of water out of the cerebrospinal fluid space into the plasma. However, as the glucose is rapidly metabolized and insulin secretion rises, the blood sugar concentration falls below the concentration of sugar in the cerebrospinal fluid; this event favors transfer of water from the plasma to the cerebrospinal fluid with rise in cerebrospinal fluid pressure. This observation has led to the abandonment of use of 50 per cent glucose in such patients.

Much the same application might be made in the case of either 5 or 10 per cent glucose in water. It has been shown that administration of either in amounts of a liter or more results in an increase in cerebrospinal fluid pressure.[2]

DOCTOR FREED: Would you explain the mechanisms of that?

DOCTOR BLAND: The cerebrospinal fluid pressure is elevated after 5 per cent glucose infusion because water moves from the plasma to the cerebrospinal fluid space; the glucose is very rapidly metabolized or converted to glycogen. Hence, a large volume of water is metabolically divested of its solute (glucose) which was responsible for its original tonicity. The added water volume to the plasma renders it hypotonic; with this decrease in osmotic pressure of extracellular water, an osmotic gradient results; this favors transfer of water to cerebrospinal fluid, resulting in a rise in intracranial pressure.

I suggest that the best solution to give intravenously to the head injury patient is 2.5 per cent glucose in 0.42 per cent saline (half hypotonic). This solution exerts little or no influence on cerebrospinal fluid pressure.

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Stress: Its Effect Upon Fluid and Electrolyte Metabolism

WILLIAM W. SCHOTTSTAEDT
ROBERT BARNES

THAT STRESSFUL SITUATIONS and emotional reactions are associated with variations in urinary volume and urinary composition is not a new observation though it has been the subject of investigation only in recent years. In 1924 MacKeith[1] reported that tension preparatory to running a race was associated with inhibition of urinary output quite similar to that seen during running itself. In the following year Mohr[2] published observations demonstrating that a marked diuresis occurred during periods of anxiety. Mohr also suggested the possibility of increasing the diuretic effect of drugs by making use of those emotional states which were associated with diuresis. These observations were extended in 1938 by Rydin and Verney[3] who concluded from their experiments that the anti-diuresis of mild exercise was a function of the stress experienced when exercise was begun. Eight years later O'Conner and Verney[4] published the results of experiments which demonstrated that sympathetic stimulation and secretion of anti-diuretic hormone were two factors in producing this anti-diuresis. Brod and Sirota[5] demonstrated a decreased renal blood flow and decreased glomerular filtration rate in rabbits during the emotional disturbance produced by noxious stimulation. And Blake[6] reported in 1951 a decrease in sodium excretion in association with exercise and "emotion" in dogs. In this same year Hinkle, Edwards and Wolf[7] reported a diuresis in normal and diabetic individuals occurring in association with feelings of anxiety, confirming the report of Mohr.

The studies to be summarized here began as an attempt to arrive at a more precise delineation of the fluctuations in renal excretion which accompany stressful situations.[8] These investigations began with a study of five healthy subjects who collected urine specimens four times a day while going about their usual daily activities. Collections were continued for 18 to 42 consecutive days. No restrictions were imposed

upon the subjects but the major pertinent variables were carefully observed. Thus the individuals recorded food and fluid intake (both the amount and time of taking them), position, activities, events of the day, and their emotional responses to these activities and events.

It was striking to observe how minor was the influence of ordinary variations in intake and physical activity upon renal excretion during short term observations under these conditions. The data for the study as a whole clearly showed that the general level of intake determined the general level of output when periods of two to six weeks were being considered; but this was not true for periods of five or six hours.

Table 1 illustrates this fact for urine volume. With a fluid intake of 300 cc. or less in the morning, morning urine volumes ranged from 75 to 663 cc.; with a fluid intake of 500 to a 1000 cc. in the morning, urine volumes ranged from 108 to 642 cc. Thus, there was a marked similarity in the ranges of output despite very different levels of intake.

MORNING FLUID INTAKE AND OUTPUT IN FOUR SUBJECTS

N	Intake	5-hour urine volume
25	0- 299 cc.	75-663 cc.
43	300- 499	78-600
34	500-1000	108-642

Table 1

Table 2 gives illustrative data for sodium excretion. It demonstrates that similar excretion rates were observed at low and high levels of sodium intake. And Table 3 demonstrates a similar phenomenon for potassium.

Since we know that sodium can exert a retaining effect upon water, one would expect that the answer to the discrepancies noted between intake and output might be explained by combining the data. In Table 4 we have taken the data from a subject studied for 42 days. Morning specimens only have been used to avoid any influence

SODIUM INTAKE AND OUTPUT IN SUBJECT No. 1

N	Intake	5-hour output
86	0- 50 mEq	5-63 mEq
46*	50-142	9-68

*One specimen omitted

Table 2

MORNING POTASSIUM INTAKE AND OUTPUT IN SUBJECT No. 1

N	Intake	5-hour output
21	0- 5 mEq	5-27 mEq
25	6-17	7-25

Table 3

of diurnal variation. There were 29 mornings with a fluid intake of 300 cc., but with considerable variation in sodium intake. The range of excretion rates is essentially similar for the observation periods with low sodium intake as for those with high sodium intake. These data are shown to document

MORNING SODIUM AND FLUID INTAKE AND OUTPUT IN SUBJECT No. 1

N	Fluid intake	Sodium intake	5-hour urine volume
15	300 cc	0-15 mEq	81-534 cc
14	300	16-45	105-489

Table 4

the statement that the immediately preceding intake has only a minor influence on output under the conditions of ordinary daily living.

Nor can one show a clear association of output with activity or rest. In Table 5 are given data relating to unusual daytime exertion or to daytime recumbency for periods of two hours or more.

Again, one notes a very similar range of excretion rates under either set of circumstances, some rates being very low and others quite high. Levels of intake are not shown in this table but combining intake

VARIATIONS IN ACTIVITY AND RENAL EXCRETION IN SUBJECT No. 1

Condition	N	(——5-hour output——) H_2O cc	Na mEq	K mEq
Quiet routine	47	153-339	19-42	10-23
Unusual physical exertion	8	96-471	4-42	14-26
Prolonged daytime rest period	10	90-519	11-40	14-21

Table 5

data with excretion rates does not affect the interpretation.

The marked variations just discussed do show a rather striking correlation with the emotional state of the individual, however, and this without regard for level of intake or amount of activity. Periods of tranquility have been chosen as a baseline for comparison with other emotional states. These have been defined as periods during which the individual was going about routine and familiar activities without awareness of any disturbing influences. Figure 1 shows com-

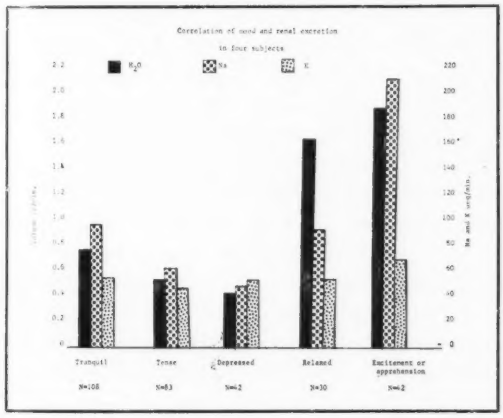

Figure 1

bined data for four of the five subjects. The fifth subject could not be included since his usual level of intake and output were much higher than for the remaining four subjects. His patterns of excretion were exactly similar however. It will be noted that feelings of tension were associated with decreased urinary volume and urinary sodium while feelings of anxiety were associated with a diuresis of the substances, as reported by other investigators. Feelings of depression were associated with a decrease similar to that seen with tension. It is of great interest, however, that periods of active relaxation were associated with a diuresis, particularly an increase in urinary volume. Potassium excretion shows little variation with these alterations in mood, demonstrating that tubular as well as glomerular influences must have been present to produce these results.

If we re-examine the data given for excretion rates during unusual exertion or complete physical inactivity with attention to the emotional state of the individual, the marked fluctuations previously noted become understandable. Figure 2 illustrates

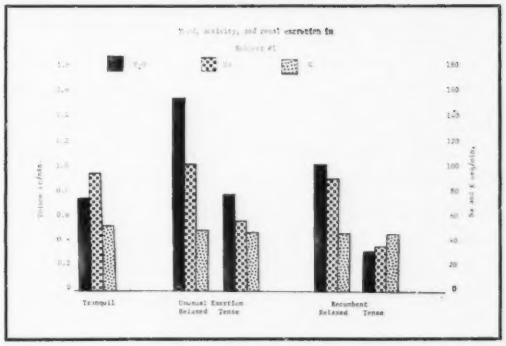

Figure 2

this well. Whether one considers the data accumulated during physical exertion or physical rest, the high excretion rates occurred when the subject felt relaxed, the low excretion rates when he felt tense.

Of equal interest is the effect of emotional states during sleep. Tension or fatigue felt at the end of the day was usually reflected in low excretion rates during the night (Figure 3). This was particularly true on those nights when the subject awakened from sleep feeling as tired and weary as he had felt the night before on going to bed. Where dreams were reported, the emotional state exemplified by the dream was often reflected in the excretion rates, suggesting that the emotion or attitude was of much longer duration than a dream is ordinarily considered to be. And where re-

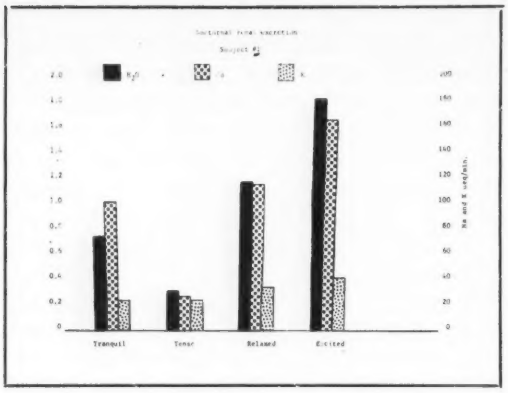

Figure 3

laxation occurred or where anxiety was present during sleep (as exemplified by dreams or by the emotional state of the subject upon retiring and awakening), excretion rates were high, exactly as had been true in the waking state.

These studies have been repeated on a metabolic ward with intake and activity carefully controlled so that the pertinent variable would be the emotional state of the individual. The frequency of stressful events and significant fluctuations in renal excretion was markedly reduced on such a ward but the associated changes in renal excretion were exactly the same (Figure 4).

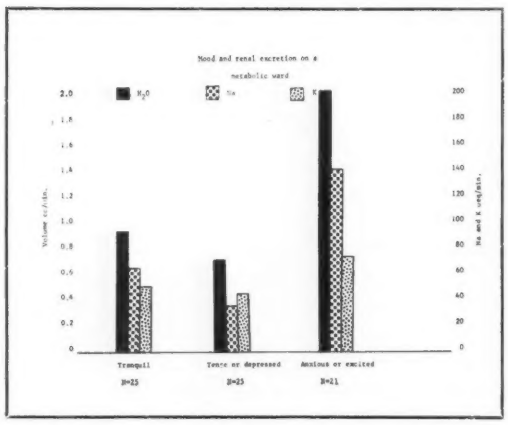

Figure 4

Again, a decrease in urinary volume and sodium excretion was observed when the subjects experienced feelings of tension or depression and a diuresis of these substances when the subject was feeling anxious, apprehensive, excited, or angry.

There are many clinical applications of these findings. The marked diuresis and loss of base which accompanies situations arousing feelings of anxiety or anger can be of major proportions. In one of our healthy subjects, an episode of intense anger was accompanied by a loss of 170 mEq. of sodium during a 5-hour period. The pertinence of this to the diabetic has been demonstrated by Hinkle, Evans, and Wolf[9] using stress interviews under controlled laboratory conditions. In one of their experiments, a diabetic subject, angered by the brusque and unsympathetic manner of her physician, excreted 1130 cc. of urine containing approximately 70 mEq. of chloride in a two hour period of observation.

There are many other clinical states in which fluid and electrolyte disturbances are important. The influence of emotional states deserves consideration in each of these. I would like to turn attention now, however, to the influence of these various emotional states on fluid and electrolyte balance in the cardiac patient who has suffered an attack of decompensation.

In 1953 Chambers and Reiser[10] presented correlations between stressful life situations and the onset of congestive failure as gained by interviewing consecutive admissions of cardiac patients. They reported two types of situations as of special importance in the precipitation of episodes of failure: 1) events which aroused feelings of rage and frustration, and 2) events which aroused feelings of rejection and loss of security. The hemodynamic changes associated with anger made the first group readily understandable to them; but they had no explanation for the second and larger group, many of whom they described as tense or depressed.

Doctor Robert Barnes has been working with us for the past year and a half to document the pertinence of emotional states and their attendant alterations in renal excretion to the status of the cardiac patient.[11] Data he has collected on one of these patients will illustrate the type of relationships which he has discovered.

This patient was a man of 43 years with hypertensive heart disease. His blood pressure as taken by his local physician remained fairly constant at a level of 210/130. His renal function, however, remained good. Intravenous pyelograms showed good renal function, his blood urea nitrogen was 18. An electrocardiogram showed no evidence of infarction or ischemia and a chest film while the patient was in failure showed a grossly enlarged heart with some enlargement of all chambers but chiefly of the left ventricle. His weight on admission to the hospital was 243 pounds, some 75 pounds above his dry weight.

During his hospital stay of 10 weeks, all 24-hour weight gains of 1½ pounds or more could be explained easily in terms of events which aroused feelings of tension or depression. On one occasion his father was hospitalized because of a stroke. He had no word about his condition for two days and gained weight during this time. On another occasion he complained that the nurses were not following their instruction properly. The resident explained that he had misunderstood and that the nurses were correct. The following day the patient apologized to each nurse who came into the room since he could not remember to whom he had made the complaint. During this 48 hour period he gained more than 4 pounds in weight. Similar events could be found accompanying each of the major periods of weight gain.

During his hospital stay he received 14 injections of mercuhydrin, 2 cc. each. Twelve of these were given during the initial 5 weeks with an accompanying weight loss of 73 pounds. His average loss in the 24 hours after each injection was 4.2 pounds but the range was from a gain of 0.8 of a pound to a loss of 7.3 pounds. All major weight losses (6 pounds or more) following mercuhydrin injections were on days where the nursing notes commented on the calmness and relaxation of the patient, not a common comment for this particular patient. Weight losses of less than one pound in the 24 hours after mercuhydrin all occurred on days when the nursing notes commented on stresses on the ward which had aroused feelings of tension or depression in the patient. The one period during which he gained 0.8 of a pound during the 24 hour period following an injection of mercuhydrin occurred on a day when another patient was moved into the room with him. This patient had been in and out of the hospital for several years, was well known and a favorite among the staff. The cardiac patient seemed to resent his presence and did everything he could to take the attention away from his new roommate. However, this occurred only a few days following the reprimand for complaining about his nursing care and during the day he told one nurse that he was afraid to complain anymore for fear of getting "kicked out."

When a stable weight seemed to have been attained, short term observations were begun. During these the patient sat quietly in his room sewing, an occupation which he enjoyed, from nine to ten in morning and from eleven to twelve. During the hour from ten to eleven a variety of observations were made. Some of these periods were spent sitting quietly in his room, some walking, others lying down, and some concentrating. One of the periods of concentration was spent sorting the cards of the Minnesota Multiphasic Personality Inventory. The others were spent on mathematics problems, since this patient had said that mathematics was particularly difficult for him.

Table 6 shows the effects on urinary excretion rates of these various activities. The patient was on a low sodium diet which accounts for the low excretion rates for this substance.

FLUID AND ELECTROLYTE EXCRETION IN A CARDIAC PATIENT

		(—Excretion—)	
		Volume	Sodium*
Conditions	N	cc/min	uEq/min
Recumbent	4	0.97	8.2
Sitting	4	0.62	2.5
Walking	4	0.40	2.4
Sitting and Concentrating	2	0.45	0.3

*Patient on a low-sodium diet

Table 6

The average excretion rates during periods of lying, sitting, and walking betwen 10:00 and 11:00 a.m. showed the decrease in urinary volume and a decrease in urinary sodium which has been reported by other observers to occur in cardiac patients when sitting or walking. It was interesting to observe one episode of sodium diuresis in this cardiac patient during an hour of walking. On this occasion he was feeling quite angry and upset about the early morning cereal which he had received. His sodium excretion rate on this occasion were more than four times the average for the other three occasion when he was walking. The most striking finding, however, was the sodium excretion observed when the patient was sitting quietly but concentrating on the Minnesota Multiphasic Personality Inventory or on mathematics. Sodium excretions at these times averaged 0.3 uEq/min., one-eighth that observed when he was sitting quietly and not concentrating.

In these experiments, the activities for the hour from ten to eleven had been determined well in advance. The patient knew each day what he would be doing during that hour. It is of considerable interest to note the variations in excretion rates between nine and ten and their correlation with what the patient was anticipating doing during the following hour. Table 7 summarizes these data. Excretion rates during the hour from nine to ten, all of which were spent sitting quietly and sewing, were quite different depending upon whether the patient was expecting to lie, sit, walk or concentrate during the subsequent hour. This difference in anticipation was the only consistent difference known to the investigators.

THE EFFECTS OF ANTICIPATION ON RENAL EXCRETION

(Patient sitting during all observations)

		(—Excretion—)	
		Volume	Sodium*
Anticipation of	N	cc/min	uEq/min
Continued sitting	5	0.53	2.1
Walking	4	0.34	1.5
Concentrating	3	0.28	1.0

*Patient on a low-sodium diet

Table 7

The mechanism by which these changes in renal excretion occur has not been adequately investigated. Table 8 shows data on endogenous creatinine excretion which indicates that glomerular influences play a role in the decreased excretion which accompanies feelings of tension and in the increased excretion which accompanies feelings anxiety or anger.[8e] It seems likely that tubular mechanisms are involved as well but these have not been investigated as yet.

CREATININE EXCRETION IN PERCENT OF MEAN OBSERVED DURING PERIODS OF TRANQUILITY

Conditions	N	Mean	S.D.
Tranquil	51	100.0	±1.9
Tense	60	84.8	±1.9
Relaxed	14	99.5	±3.6
Anxious, excited, or angry	38	110.4	±3.2
Depressed	18	90.4	±2.2

Table 8

In conclusion it should be emphasized that there is nothing mysterious or occult in the common observation that emotional reactions affect the course of a patient's illness. These responses evoke the same mechanisms which are utilized by the body to meet physical stresses. At times these mechanisms operate to maintain or to restore homeostasis, as when the diuresis of relaxation helps rid the patient with cardiac failure of excess body fluid. But these same mechanisms may, under other circumstances, lead to serious derangements of bodily economy requiring for their correction the interest and the therapeutic efforts of the physician.

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DISCUSSION

DOCTOR FREED: Doctor Barnes, a series of questions: Do you have any findings on urinary hormones in your patients? And the other question is, since many of us may not be adept in controlling the moods in our patients, is there a possibility of utilizing tranquilizing drugs to alter water and electrolyte metabolism?

DOCTOR BARNES: In answer to the first question, we did not do any of these; however, we are planning on studying aldosterone levels in reference to this problem. This may be very pertinent. We have seen in some other studies that at the time of the production of anger, a very significant rise in blood pressure of probably 30 to 40 mm. of Hg both systolic and diastolic. With this raising the blood pressure, there was an associate increase in urinary sodium. It would be very interesting to see if this is associated with alterations in aldosterone excretion.

In the American Heart Journal[1] there was an article on the diuretic effect in the tranquilizers. It would be very easy to see that the use of a tranquilizer in a patient who is very frequently discouraged and depressed could result in a change in urinary sodium, which would be beneficial. However, I don't believe that tranquilizers are necessary since a very short conversation with the patient will frequently result in these changes. One example of this was a young patient with rheumatic heart disease and an unexplained 3-day retention of sodium. The explanation of this situation came only after the patient's wife had called at the end of this 3-day period and said that "Three days ago you increased the digitalis in my husband—we both realize that his heart is very much worse now." After explaining to the patient that an increase in the dose of digitalis did not mean his heart was any worse, there was a prompt increase in the sodium in the urine.

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Role of the Connective Tissue System in Water and Electrolyte Metabolism

JOHN H. BLAND

Introduction

AN IDEA held for many years—and sometimes still held—is that connective tissue is an inert stuffing material, filling up body spaces, involved in physiology to the extent that it holds cells and organs together. Analysis of function of connective tissue is largely yet to be done.

Extravascular, extracellular space is filled with specialized cells, fibrillar elements and a complex reactive gel, whose physical and chemical properties are sensitive to its environment. Extracellular tissue space is not a void through which water and salt trickle freely. Little is known concerning transport or storage of water and dissolved solids in connective tissue. Important and provocative beginnings have appeared in the study of movement and storage of ions, water and other substances through the connective tissue barrier.[26, 27, 17, 18, 19] I'd like to review some of this data as it relates to water and electrolyte metabolism.

Role of Connective Tissue System in Water and Electrolyte Metabolism

In water and electrolyte consideration we speak as though we deal with definitive spaces—as though the body is a water bag with one or two smaller water bags inside. Are there organs or tissues as reservoirs of water and electrolyte? Does electrolyte and water accumulate in some tissues with preference to others? Most studies have dealt with muscle tissue—but muscle constitutes only 40 to 50% body weight. When measuring inulin space we measure some water space but don't know really what it is. We call it inulin space. Someone said that inulin space measures inulin space.

When normal tissue from which blood has been drained is cut no fluid escapes. The tissue looks moist. It contains more than half its weight of water. We deal with something that resembles a jelly more than a water-filled sponge.

Protoplasm has long been considered a

gel. On further consideration the extracellular supporting tissues are in the gel form.[1] It has been suggested that firmness of the gel depends mainly on magnitude of polymerization of glycoprotein. The degree of polymerization (and firmness or stiffness of the gel) varies widely from tissue to tissue—organ to organ; and at different times and different physiologic and pathologic states in the same tissue; from a tissue of the rigidity of bone to one of the softness of loose connective tissue. In rapidly growing tumors or in the symphysis pubis of pregnant guinea pigs the "ground substance" is more fluid-like, less polymerized than normal.[2] Ordinary edema, is associated with the appearance of watery fluid. Transformation from gel to sol is, however, incomplete. Clinicians record a different "feel" of edematous tissues from one case to another. Water, small molecules and ions diffuse rapidly through gels. Larger molecules such as inulin move slowly. An inulin infusion equilibrates with extracellular fluid in about five hours.[4] Hypertonic salt diffuses through extracellular space in twenty minutes.

Connective tissue is ubiquitous—present in varying forms in all tissues; a clearer picture of its capabilities, function and reactivity is emerging. While glycogen deposits accumulate in the enzymatically active interior of the living cell, most mucopolysaccharides are extracellular substances, covering cell surfaces and occurring in large amounts in intercellular spaces. Intracellular glycogen deposits change continuously during the course of many physiological processes; mucopolysaccharides are renewed at a relative slow rate. Amount and distribution of these substances remains rather constant under physiologic circumstances; their importance to the maintenance of animal life becomes apparent in disease. Research in recent years, based on chemical and histochemical methods, has shown that mucopolysaccharide production by the living cell and distribution of these substances in tissues and body fluids is altered in many states of disease and trauma.

Connective tissue fills spaces between cells and blood vessels; serves as a filter bed for nutrients, water, electrolyte and other metabolites passing to and from cells. No true interstitial "space" exists. Normally extracellular gel or ground substance fills all space between cells and groups of cells.

The Nature of Connective Tissue

Composition of connective tissue elements varies quantitatively, and in some instances qualitatively. The microscopic structure is that of cells and fibrillar components lying within a ground substance gel. Cell function depends on properties of this gel; alteration taking place within this milieu, chemical or physical, can profoundly influence nutrition and metabolism of the cell. Figure 1 lists the three basic connective tissue components.

CONNECTIVE TISSUE COMPONENTS

CELLS	EXTRACELLULAR FIBERS	MATERIAL MATRIX
1. Fibroblasts Or Fibrocytes	1. Collagen	1. Protein
2. Histiocytes	2. Reticulin	2. Polysaccharides of hyaluronic acid type and their sulfuric acid esters
3. Mast cells	3. Elastin	

Figure 1

The fundamental connective tissue system is regarded as a continuous gel matrix in which lie cells and an interlacing fabric of fibers. Parenchymal cells, bathed in matrix, may be isolated or closely set, oriented to serve a special function; renal tubules for reabsorption and secretion; skeletal muscles, nervous tissue, blood or lymph vessels with their special functions. Where connective tissue provides support only for cells, the intercellular substances consist mainly of soft matrix and reticular fibers; tendons and ligaments providing great tensile strength are composed mostly of collagenic fibers and very dense matrix-cement substance; bone and cartilage have the fibrous elements solidified by considerable amounts of cementing type (highly polymerized ?) matrix. This complex of fibers and cement substance provides a medium suitable for precipitation of calcium salts providing even more rigidity.

The nature and thickness of the connective tissue layer varies from organ to organ. In lungs and endocrine glands it is very thin; in liver and kidneys it is thicker; in heart and skeletal muscle it forms a very significant part of the organ; such is also true of intestinal tract and skin; bones, joints and tendons are formed almost entirely of connective tissue. Connective tissue is continuous throughout the body. An organ or structure is characterized by the relative amounts of the three basic connective tissue structures in its make-up, cells, fibrillar elements and ground substance.

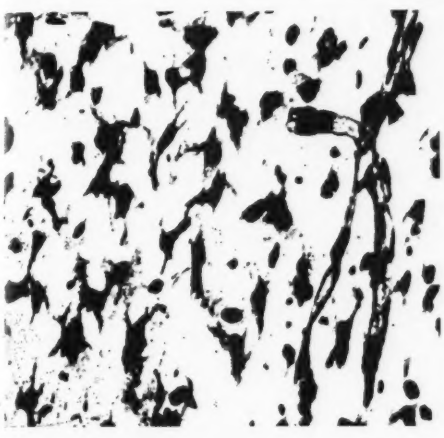

Figure 2. Normal human connective tissue stained by silver impregnation. Gray cytoplasm and black nuclei of fibrocytes is seen. White spaces filled with fibers and ground substance.

Figure 2 illustrates normal human loose connective tissue stained by silver impregnation. The gray cellular component, fibrocytes, is seen as gray cytoplasm and black nuclei. The white spaces are filled with fibers and ground substance.

Cells: Cells of normal connective tissue are elongated fibrocytes with irregular, branching, cytoplasmic processes, building up a sponge work, the meshes of which are filled with matrix and fibers. Tissue mast cells and histiocytes may be present.

Fibrillar Elements: The three fibrillar elements are collagen, reticulin, and elastin. Collagen fibers are largest and most abundant. Collagen fibers are in bundles of parallel fibrils. Collagen is a protein. It swells more in acid solutions than any other protein. It is nearly insoluble in water but on heating is converted to a water soluble substance—gelatin.

Ground Substance: Ground substance is the extracellular, extra-fibrillar amorphous matrix of connective tissue. Certain components are probably derived from the fibroblast. These are acid mucoprotein, acid mucopolysaccharide and dispersed or soluble collagen (pro-collagen). Other components not locally derived include water, electrolytes, small organic molecules (e.g. glucose and urea) plasma proteins and cell metabolites. Ground substance is unfortunately often equated with acid mucoprotein and acid mucopolysaccharides; however on a quantitative basis and may be on a functional basis such other constituents as neutral mucoproteins, plasma proteins and soluble collagen are more important.

Many presumably distinct mucopolysaccharides of connective tissue have been identified, the principal ones are hyaluronic acid, the various chondroitin sulfuric acids and heparin. These are all polymers of high molecular weight, composed, among other moieties, of hexosamines (glucosamine for hyaluronic acid and galactosamine for chondroitin sulfate) and glucuronic acid. Figure 3 illustrates a repeating unit of chondroitin sulfate.

Metabolically mucopolysaccharides are slowly turned over. When one considers that all materials entering and leaving cells must move through the ground substance, its importance is evident. It has been sugtural elements exerting an influence on the

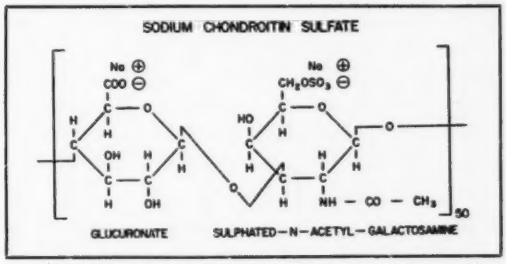

Figure 3. Note the glucuronic acid with a free anionic group capable of binding a cation to form a neutral salt. The galactosamine can likewise accept a cation. There are considered to be about fifty such repeating units in a chondroitin sulfate molecule.

gested that mucopolysaccharides function like a reactive gel, like an ion exchange resin, binding and releasing ions.[17, 18, 19, 26] Theoretically changes in concentration or state of polymerization could alter connective tissue capacity to bind inorganic ions and water. Hyaluronic acid is very hygroscopic and could exert water binding function in the tissues. Study of body fluids is incomplete without consideration of gels, that evasive and pervasive ground substance, in which water and electrolyte is in storage and transit.

It is convenient to subdivide amorphous intercellular substance into ground substance and cement substance. Ground substance is a term used for sols or soft gels and cement substance refers to more concentrated and rigid gels.

The body is commonly described as a great community of cells. It is more accurate to describe it as an edifice of intercellular substance in which the cells live as residents. Cells are jelly-like. The form of the body is due largely to its content of these stronger and non-living materials that are disposed between cells. Connective tissue not only connects the individual organism into a functional whole but as Doctor Asboe-Hansen of Copenhagen has said, "Connective tissue connects the numerous branches of medical science. Without connective tissue medicine would come to pieces, non-viable pieces, like cells of the human body would come apart without connective tissue."

Metabolic Movement Through Capillary Walls to Surrounding Connective Tissue

The capillary wall acts as a semi-permeable membrane allowing free passage of water and solutes, with a diameter below approximately 100 angstrom units. However, permeability of this barrier may increase; even cellular constitutents of blood penetrate into surrounding connective tissue.

Considerations of blood-tissue interchange place insufficient emphasis on the multiple nature of the capillary barrier. The capillary wall proper (endothelial cells and the cement substance) is only a frame work on both sides of which are superimposed structures. Five distinct structural elements are encountered as water and electrolyte cross the capillary and enter surrounding connective tissue.

(A) Proteinaceous film-like component lining the capillary (? from plasma or platelets).

(B) Endothelial cells proper.

(C) Intercellular cement substance.

(D) Condensed capillary sheath.

(E) Connective tissue proper including the ground substance and its fibrillar constituents.

Movement of substances across the capillary barrier is governed by such physicochemical forces as:

(A) Concentration and hydrostatic pressures.

(B) Pore size of component structures.

(C) Thickness of each structural component.

(D) Molecular diffusion characteristics.

(E) Lipid solubility of involved materials.

The capillary surface is an extensive cellular area with less than 1% intercellular zone. Does the bulk of exchange occur across the entire capillary surface? Is it restricted to the more permeable intercellular cement?[6] Pappenheimer,[7] from studies with isotopes, suggests that small molecules, water and electrolytes diffuse in and out of the capillaries through an extremely small area of total available surface.

Inner Layer: The inner proteinaceous layer closely adherent to endothelium and cement substance, is so thin as to be usually invisible by microscopy. It seems to represent a blood constituent absorbed on to these surfaces. Its nature is not established. The evidence for its existence is indirect in nature. The concept arose from microscopic observations in mesenteric capillaries of living animals. This capillary lining is a labile entity readily altered in functional and pathological states. Zweifach[8] suggests that some edema states attributed to change in colloid osmotic pressure and protein depletion may be ascribed to alteration in the protein layer.

Experiments in perfusion of the capillary

system with colloid free mixtures have shown that the protein lining of the vessel could be "washed out"; progressive edema follows.[12] Perfusion medium manipulations (other than addition of colloid or protein) do not restore permeability. Small amounts of colloid have a restorative effect on permeability out of proportion to their osmotic pressure values. Electrolytes solutions are ineffective in restoring the protein lining.

Intercellular Cement: The basic structure of intercellular cement substance is presumed to be a dense, highly polymerized substance, probably a mucopolysaccharide protein complex. A large molecular component is superimposed on it by electrical, chemical or surface tension forces plugging most large pores, reducing overall perviousness of the structure. Pore size, number and shape of pores are thought to be determined by the physico-chemical nature of the cement and its absorbed component.

Cement substance is a labile structure with variable physico-chemical make up. It may be in a continuous state of change. The nature of the cement is affected by changes in electrolyte concentration. Calcium is essential for maintenance of normal characteristics of this material. Calcium excess seems to increase cement substance. In rat and rabbit mesentery under microscopic observation, perfusion experiments with calcium free perfusate have shown cement to go into solution and wash away.[6] Acid pH of perfusate results in dissolution and washing away of cement. Loss of cement is followed by progressive edema of surrounding tissues.[8, 23]

In tissue culture preparations endothelial growth in sheaths or tubes is dependent upon the presence of adequate amounts of calcium. If calcium content of tissue culture media is reduced the endothelial sheath begins to fall apart, cells move away from one another and round up. With re-introduction of calcium these cells again flatten out and join to form a continuous sheath or endothelial tube.[9, 10] A small amount of calcium, about 10% of normal, is enough to maintain some adhesiveness.

Absence of adhesive cement substance in calcium free media does not necessarily indicate that material is not being produced; it may be secreted in a soluble state.

It seems significant that a structural element, cement substance, constituting only about two tenths of one per cent of the entire capillary surface, represents the major factor effecting the bulk of the exchange, water and electrolytes, between blood and tissues.[7] Pappenheimer[7, 11] on the basis of hind limb perfusion studies, concluded that exchange of water and lipid insoluble materials (electrolytes) must occur across an extremely small fraction of the total capillary surface. Oxygen, carbon dioxide and lipid soluble materials probably permeate through the cell surface.

Endothelial Cells: Capillary tone or elasticity is a reflection of tone of the endothelial cell itself. This property depends considerably on the cell's water content. Injection of hypotonic solutions in tissue adjacent to capillaries causes them to swell. This may proceed to obliteration of the lumen. Micro-injection of hypertonic solutions causes endothelial cells to shrink away from one another—to the point of leakage of red cells through spaces between cells.

Zweifach[23] has by micropipette introduced silver nitrate into capillaries. This causes blackening of the intercellular cement. Excessive concentrations irreversibly damage the endothelial cell. Then no regeneration of cement material occurs. Endothelial cells may serve the important function of replacement of intercellular material; secretion is postulated.

Perivascular Sheath: The last feature of the capillary wall is the sheath of fibrils embedded in ground substance, closely applied to the outer endothelial surface. It varies in thickness and consistency in different parts of the vascular system. This condensation of connective tissue ground substance presents a barrier to water and electrolyte to and from the capillary lumen. Leukocytes and red cells under experimental conditions enter the area between endothelium and capillary sheath.

Important changes in the peri-capillary sheath occur. In scorbutic guinea pigs the sheath is readily ruptured by micromanipu-

lations with extravasation of material from blood into peri-capillary connective tissues. Two events occur in scorbutic pigs:

(1) Weakening of the perivascular sheath, probably resulting in fragility of vessels.

(2) Cement substance later becomes deficient.

Hyaluronidase introduced by a micropipette on the vessel wall results in erosion at this point and petechial hemorrhage. Hyaluronidase has no visable effect on cement substance inside the capillary. This supports the concept that cement and ground substance are two distinct chemical entities.[24] There is the impression that common forms of increased capillary fragility are due to biochemical changes in the pericapillary layer.

The importance of components of the capillary wall in water and electrolyte exchange between blood and tissues is emphasized. It has been suggested that thinness is the factor permitting the cell to act as a permeable porous barrier. This seems fallacious. There are many examples of thin layers of protoplasm maintaining a selective type of permeability. Evidence concerning endothelial cell metabolism indicates that it duplicates metabolic phenomena of other living cells. Until there is evidence to the contrary, it is reasonable to assume that endothelial cell permeability characteristics are like those of other cells. This requires explanation other than cellular permeability as the primary consideration in capillary permeation and exchange of materials from blood to tissues.

Movement of Water and Electrolyte Through Connective Tissues

Final structural component of blood-tissue exchange is connective tissue proper. Injection of diffusible dye into ground substance results in rapid, even diffusion, as when dyes are introduced into a gelatin block. Several conditions could limit free movement of water and electrolyte in this medium — or accelerate it. The gelated ground substance can be transformed toward a sol by factors to be discussed (accelerate movement water and electrolyte). Avidity for cations of both fibrous elements and ground substance may change and in turn alter avidity of these structures for water.

I'd like to raise some questions and speculate on some ideas regarding movement of water through connective tissue. Water might move between or along fibrils, in thin layers or films, so thin that water is no longer free but held to fibrils by surface forces; like a fluid film between two plates of glass; captured, unable to move freely but still a fluid, not part of the ground substance, still capable of behaving chemically as a fluid—able to transport ions and diffuse into cells. Such fluid films would be spread more rapidly along fibrils by mechanical squeezing of tissue elements as occurs with dye.

Do electrolytes move through the fluid? Or are they loosely, chemically combined, as in an exchange resin, in the ground substance? (See Figure 3.) What is the relationship of the fibrils to fluid and electrolyte transport?

Collagen can take up water and swell immensely. There are great numbers of connective tissue fibers in nearly all tissues. Millions of fibers must present an enormous surface area upon which water may exist. This could account for the fact that measured extracellular fluid volume is as large as reported, amounting to nearly 30% of all the body fluid.[13,14]

Gaudino[15] has done some illuminating experiments relating to desoxycorticosterone and its possible influence on connective tissue and the fluid spaces. He used the techniques of inulin and heavy water (D_2O) space measurements. Figure 4 summarizes the first set of these experiments.

In dogs during DCA administration (30 mgs./day) inulin space increases progressively; D_2O space (total body water) remains approximately normal or decreases slightly; intracellular water volume decreases; interstitial space (containing the connective tissue) increases markedly; and plasma volume decreases slightly or remains unchanged. These changes tended to return to normal despite continued DCA adminis-

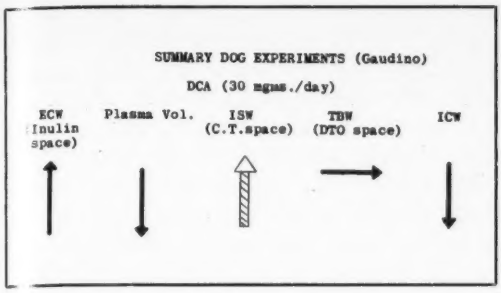

Figure 4

tration at about the 11th day. Sodium seems to move from interstitial connective tissue to an intracellular position after DCA treatment. Serum potassium fell to half the control values.

Adrenalectomized dogs were maintained on 15 mgs. of DCA per day; they showed no signs of adrenal insufficiency. Measurements of the total body water (D_2O space) and inulin space were the same as those in the normal animal receiving DCA.

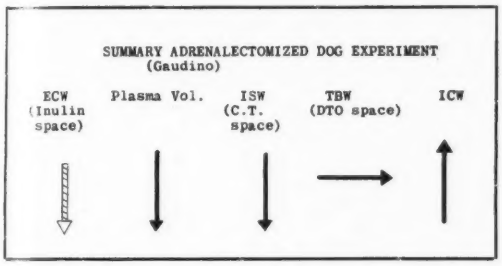

Figure 5

Figure 5 illustrates the following events: therapy was discontinued; inulin space progressively decreased but total body water did not change; inulin space declined an average of 50% from control values; total body water did not change; intracellular water increased to 30%. As inulin space declined, glomerular filtration, and PAH clearance were markedly and progressively reduced until the animals died. Blood potassium concentration increased; sodium concentration decreased; the BUN rose; specific gravity and hematocrit rose.

In these adrenalectomized animals plasma volume remained at control values during *early mild degrees of insufficiency;* changes in the other compartments were common. It appeared as if in early adrenal insufficiency plasma volume and intracellular volume were maintained at the expense of interstitial space.

The experiments suggest that DCA has an influence on maintaining and expanding interstitial space (containing connective tissue) possibly by some as yet unidentified influence on connective tissue fibrils or matrix. DCA stimulates collagen formation which may be a factor.

The question of capability of the ground substance or collagen to bind water remains unanswered. There surely are degrees of water binding in interstitial space. Bound water, has been defined as water which though fixed in place, can be molecularily exchanged. The term "bound water" should be reserved for water unavailable as a solvent and not considered in measuring activity or osmotic concentration. Forces binding water are unknown.

Doctor Karl Meyer postulates that fibrous structures are hydrated; that the structures are colloids and that water phase will bind certain ions without serving as water of solution; that it will bind sodium, chloride and potassium in readily exchangeable form.

From these considerations, it appears that an important and little known function of connective tissue is that of being a buffer compartment, a depot; an avenue of exchange for water, electrolytes and other substances necessary for cell metabolism or resulting from it. If interstitial space is composed mainly of connective tissue this would clearly appear to be one of the main functions of connective tissue.

Ground Substance as Polyelectrolyte*

Ground substance of connective tissue contains three components:

(1) Colloids

(2) Diffusible electrolytes

(3) Water

The polyelectrolyte nature of the anionic polysaccharides of connective tissue sug-

*A highly aggregated, high molecular weight molecule with varying anionic or cationic charge density, capable of binding cation or anion depending on its charge, e.g. Chondroitin sulfate, a salt of molecular weight 20,000 to 30,000, often isolated with sodium or potassium as its cation; polymer consists of about 50 repeating units, which, if completely ionized could carry a total negative charge of 100 units per molecule. As dry neutral salt, this charge is balanced by 100 equivalents of cation, sodium or potassium.

gests that they may bind cations. Since hyaluronic acid and the chondroitin sulfates constitute such important components of connective tissue, the binding properties of these polyelectrolytes may influence distribution and storage of extracellular cations. Furthermore changes in extracellular polysaccharide (e.g. depolymerization) metabolism might influence the course of diseases in which storage and distribution of sodium play a major role.

The amounts of water and electrolyte in the ground substance depends on its electrochemical properties. One measurable property is the charge density of cation or anion binding groups of immobile colloids. This quantity may be estimated as equivalents per kilogram of tissue water. Catchpole, Engel and Joseph[17,18,19] measured electrical charge density using the liquid junction potential method. They further measured the effect of certain hormones on interaction of sodium, potassium, calcium and magnesium in living connective tissues.

In normal pubic symphysis of guinea pig, the charge density is high and water content low. In the relaxed (?depolymerized) symphysis pubis of the pregnant guinea pig, the charge density is low and the water content very high. Mobility of potassium is very high in relaxed state. Interaction of the negatively charged ground substance (chondroitin sulfuric acid) with sodium and potassium favors selective absorption of potassium in preference to sodium.

Calcium content of tissues other than bone is related to the density of the negatively charged ground substance of the tissue. Highest values for ionic and bound calcium are found in dense connective tissue. Hormones act on connective tissue to vary the state of ground substance aggregation; it is expected that this will affect distribution of calcium, which it seems to do.[17] There is a high affinity between calcium and chondroitin sulfuric acid. Dense tissues, e.g. cartilage, contain ionic calcium in concentrations three times that of blood while bound calcium concentration exceeds blood values by 10 times.[17]

The total potassium content of connective tissues, like the total calcium, depends on the state of aggregation of the matrix, colloids. Loose connective tissue with high wat r content, containing small amounts of ins - uble highly aggregated colloid have pot - sium and calcium concentration approac - ing that of blood; but in cartilage, pot - sium concentration is more than ten tim s that of blood and total calcium is conc - trated almost to the same extent.[17,18] Sm l increases in blood potassium seemed to r - sult in increases in ground substance pot - sium, possible displacing sodium and c - cium. At any rate inorganic composition f ground substance was responsive with var - ing sensitivity to changes in blood electr - lytes—those that can enter the matrix a d react with colloid.

Current theory suggests that glycoprotein disaggregation and formation of water soluble fractions are features of hormone action on connective tissues. Potassium is immobilized by dense connective tissues which thus act as ion exchange resin for potassium. In loose connective tissue, or in those loosened by hormonal action, colloidal charge density is decreased. Consequently relative mobility of potassium as compared with sodium increases from its low value in dense tissues to much greater mobility in loose tissues, the latter approaching its mobility in water. Thermodynamic properties of ground substance show a strong tendency for potassium to displace sodium from the colloidal phase.

It is apparent that connective tissue components, ground substance and fibers are involved in tissue permeation and in water-electrolyte, acid-base and osmotic equilibria. Interestingly, Schade[20] in 1923 published a paper proposing a theory similar to Catchpole's modern one. He formulated a regulatory role for collagen fibers and ground substance in water and electrolyte metabolism. He showed specific ions to have some influence on the colloidal state of connective tissue. Increase in sodium concentration was accomplished by increased colloid dispersion and water retention; accumulation of potassium or calcium was followed by shrinkage and loss of fluid.

Hormone Action on Connective Tissue

Organ and tissue responses to hormone action shows evidence of connective tissue participation.

The following hormonal effects on connective tissue have been observed: The hormones cortisone, hydrocortisone and corticosterone act on all components of connective tissues, cells, fibrils and ground substance.[28] Fibroblasts are reduced in number.[28,29] Collagen production is reduced.[28] Permeability of ground substance is decreased.[30]

Growth hormone increases fibroblast proliferation and formation of collagen fibrils.[31] Granulation tissue becomes abundant. Collagen formation in skin and muscle increases.[32]

Thyrotropin has a direct effect on connective tissue.[33] Injection of thyrotropic hormone causes accumulation of water binding hyaluronic acid in retrobulbar tissue and consequent exophthalmos.[33,34] Injection of thyrotrophic hormone in the guinea pig is rapidly followed by a transport of fat from normal depots to muscles, liver and kidney.[33] Mucopolysaccharide accumulation has been experimentally demonstrated in peripheral muscles, in the peri-renal and axillary regions.[33] These changes occur in intact as well as thyroidectomized animals. Thyroxin inhibits thyroid stimulating and exophthalmic effect as well as the fat mobilizing effect of thyrotrophin. The effect of thyrotrophin on connective tissue seems opposite to that of cortisone. Cortisone exerts a distinctly inhibitory effect on connective tissue elements, cells as well as ground substance; thyrotrophin has a stimulating effect with increase in hyaluronic acid.

Thyroxin has no known effect on connective tissue.

Estrogens influence the connective tissue with most emphasis on the ground substance, inhibiting permeation of electrolyte, water and dyes. Intercellular fluid is increased, presumably due to increased formation of hyaluronic acid though this remains unproved.[35] Women often become slightly edematous immediately before a menstrual period. At this juncture estrogen excretion in the urine increases. Weight is gained and the daily output of urine is decreased for a few days, consistent at least with water retention.

Testosterone renders connective tissue looser and less compact. Collagen bundles become separated by increased amounts of matrix. This material is hyaluronic acid (experiments on cock's comb).[36]

Many endocrine diseases involve change in mesenchymal tissues directly, e.g. myxedema, thyrotoxicosis, malignant exophthalmos, adrenal insufficiency, acromegaly, Simmond's disease and Cushing's disease. Connective tissues have been clinically considered important in endocrine diseases as those noted and the obvious rheumatic diseases. The fundamental changes here described suggest that connective tissue is a reactive, actively metabolizing tissue, playing an important part in water and electrolyte regulation. The binding of cations by the anionically charged connective tissue polysaccharides probably has physiologic importance. There is good reason to implicate connective tissue constitutents as possible areas of storage of osmotically inactive sodium in certain disease states in man.

It is the ambition of this presentation to suggest an attitude toward and interpretation of the little available information on the metabolic relationship between connective tissue, water and electrolyte. The stuffing is alive.

In studying and contemplating such delightfully slimy substances as hyaluronate and chondroitin sulfate I am reminded of a wonderful poem by Rupert Brooke. It is called Heaven. Essentially it is a fish's prayer. As one reads the poem he visualizes a fish, replete with flies, lolling away his noon hour on the bottom of his brook. He is glorying in the marvelous mud, water and slime all about him. He contemplates his long range future—is there a great by-and-by for fish? Surely there is an even better world Beyond. Water and slime are such wonderful things for fish and men. I'd like to quote a few lines.

> One may not doubt that, somehow, Good
> Shall come of water and of mud;
> And, sure, the reverent eye must see
> A purpose in Liquidity.
> But somewhere, beyond Space and Time,
> Is wetter water, slimier slime!

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The Metabolic Response To Injury

CURTIS P. ARTZ

INJURY, irrespective of type, initiates a series of physiologic events, effecting every organ and probably every cell in the body. In general, the magnitude of the metabolic derangements is in direct proportion to the extent of the stimulating injury. The response of the organ systems of the body is a continuing one and may cover a period of days or weeks in accordance with the type and magnitude of the trauma and the state of the individual at the time of injury.

Injury, whether it may be a surgical operation, mechanical trauma, or a burn, stimulates the central nervous system and the adrenal medulla (Figure 1). The adrenal

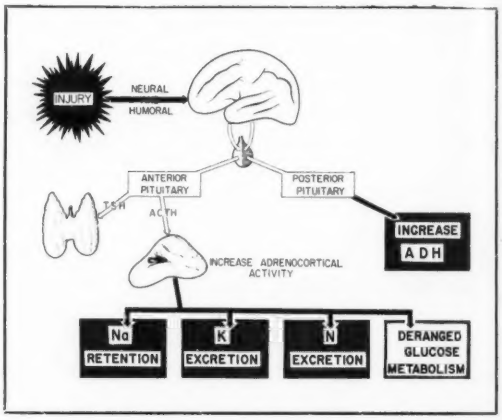

Figure 1. Schematic outline of neuro-endocrine changes and the resultant derangements occuring after injury.

medulla secretes increased amounts of epinephrine and norepinephrine. Stimuli from the central nervous system and the adrenal medulla effect the hypothalamus, which in turn stimulates both the anterior and the posterior pituitary. The anterior pituitary releases two important hormones, adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH). The posterior pituitary secretes an increased amount of antidiuretic hormone (ADH).

Although several mechanisms may be involved in the stimulation of the adrenal cortex, the degree of the response is largely dependent upon the rate of release of

ACTH by the anterior pituitary. With this release of increased ACTH soon after injury, there is a consequent increase in adrenocortical hormone excretion. There is a prompt rise of 17-hydroxycorticosteroids in the plasma. The 17-ketosteroid excretion in the urine rises but soon falls. The 11-oxycorticoids are increased in the urine, and this increase may persist for several days. Typical responses after various types of injury are shown in Figure 2. After gas-

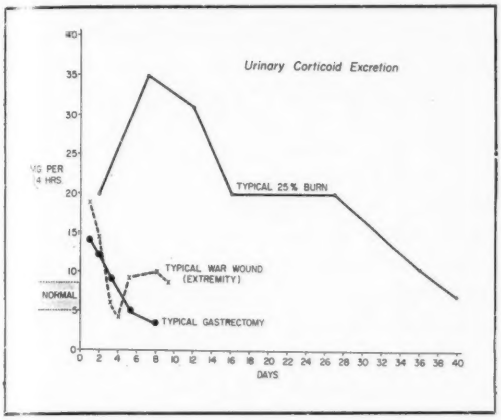

Figure 2. Urinary corticoid excretion in typical cases of various types of injury. The curves of the 25% burn and the gastrectomy were plotted from data of References 2 and 3. The curve of the typical war wound was plotted from data in Reference 1.

trectomy there is an immediate rise in the urinary corticord excretion, which usually falls to normal in six or seven days. In more severely injured patients such as those with large war wounds of the extremities, there is a more pronounced rise immediately after injury, which falls to normal after eight or ten days, unless there are secondary operative procedures or retained dead tissue. The rise in 11-oxycorticoid excretion in burns is more marked. There may be considerable increase in excretion in the first eight or ten days, which then diminishes for a period, but does not reach the normal range until well along in the convalescent period after the 35th or 40th day. When infection supervenes, urinary corticord excretion is increased and may show an increase for prolonged periods of time.[1,2,3,4]

The release of increased amounts of adrenocortical hormones and antidiuretic hormone have a pronounced effect on the sodium, potassium and water balance, as well as protein metabolism. The various adrenocortical hormones promote sodium retention, increased potassium excretion, increased nitrogen excretion and deranged carbohydrate metabolism. After injury there is a prompt antidiuretic effect mediated through the increased secretion of ADH by the posterior pituitary. There is an increased secretion of thyroxin by the thyroid gland, presumably due to increased pituitary output of thyrotropic hormone. The oxygen consumption and metabolic rate of an individual after trauma are elevated. This elevation may continue until wound healing is almost complete. One of the clinical corollaries of this increased metabolic activity occurs in burns. The pulse rate of burned patients remains above 100 until the wound is almost completely grafted. This persistence in increased pulse rate is a very consistant finding and probably represents a manifestation of increased metabolic activity until the wound is closed.

Electrolyte and Water Metabolism

Abrupt disturbances in electrolyte and water metabolism occur immediately after injury. Changes in the distribution of water occur by the early migration of fluid into and around the injured area. There is an increase in the interstitial space. Serum sodium and chloride concentrations drop immediately after injury, as there is a shift of sodium into the injured cells with an outward shift of potassium from the cells. With the expansion of the interstitial space, there is dilution that also causes a fall in serum sodium. It is well recognized that a mild hyponatremia is associated with a favorable response in severely injured patients. Sodium excretion is low initially resulting in an early positive balance, but later during the period of redistribution of fluid and resorption of wound edema, the balance becomes negative. Potassium balance is usually negative in the few days following injury, but positive balance is gradually obtained as potassium intake is increased. Generally the periods of sodium and potassium changes are considerably shorter than changes in protein metabolism. The volume

of sweat secreted is often reduced during the early postoperative period, and the electrolyte concentrations in the sweat vary in the same direction as do those in the urine. Sodium and chloride are diminished, and potassium increased. These alterations also occur in saliva.

The cumulative sodium balances in two types of injured patients are shown in Figure 3. There was a marked accumulation of sodium in the 45% burn during the early days after injury. This positive accumulation of sodium continued for eight or nine days, then as redistribution of fluid and an outpouring of water and sodium occurred and the cumulative sodium balance became negative. In the patient with the bilateral below-knee amputation there was a slow accumulation of sodium which continued for ten days, at which time a secondary operation undoubtedly was the stimulus for continued sodium accumulation.[5,6]

The cumulative potassium balances of the two patients shown in Figure 3 are plotted in Figure 4. In both the 45% burn and the bilateral below-knee amputation there was marked negativity of potassium balance during the first 12 days after injury. As more potassium was given, the cumulative balance approached zero.[5,6]

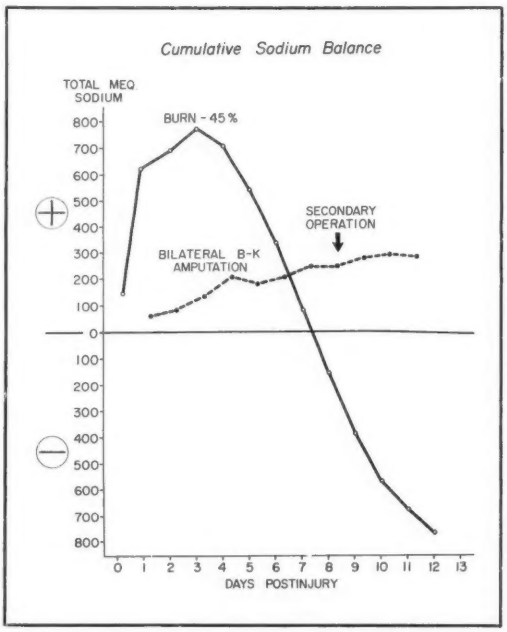

Figure 3. Cumulative sodium balance of a 45% burn and a bilateral B K amputation. There was a positive balance in the burn soon after injury which became negative after several days. The positive balance seen in the amputation probably would have fallen to zero had it not been for the additional stimulation of the second operation.

During the early postinjury phase, the outpouring of potassium may be correlated well with nitrogen losses but in some patients the early urinary potassium losses may far exceed the amount expected from determination of nitrogen losses. At the end of the first week potassium retention usually follows potassium intake. At this time potassium and nitrogen balances are completely disassociated. The daily potassium balance becomes positive, and the nitrogen balance is almost always negative. After the first two weeks the level of potassium intake has little influence on the potassium balance. Potassium balance usually becomes negative and remains slightly negative until the nitrogen balance becomes positive.[7]

The average fluid intake and urine output in 24 severely burned patients are plotted in Figure 5. The fluid intake is usually quite high immediately after injury and falls after the second day. The urinary output is quite low at first and then increases until the excess amount of water that has accumulated has been excreted. If it is assumed that the daily insensible water loss is approximately 2000 cc., and this is added to the urinary losses, the output of water will equal the intake about the third or fourth day, and eventually will exceed the intake of water on the tenth or eleventh day. In less severe burns diuresis occurs much earlier.

The daily water balance (non-cumulative without correction for insensible loss) in a severely injured patient is shown in Figure 6.[1] A greater intake than output is seen in the first few days after injury. Later a diuresis occurs with output being considerably greater than intake. The diuresis may start on the third or fourth postinjury day in moderate injuries, or take place slowly from the eighth to twelfth day in more severe forms of trauma, particularly burns.

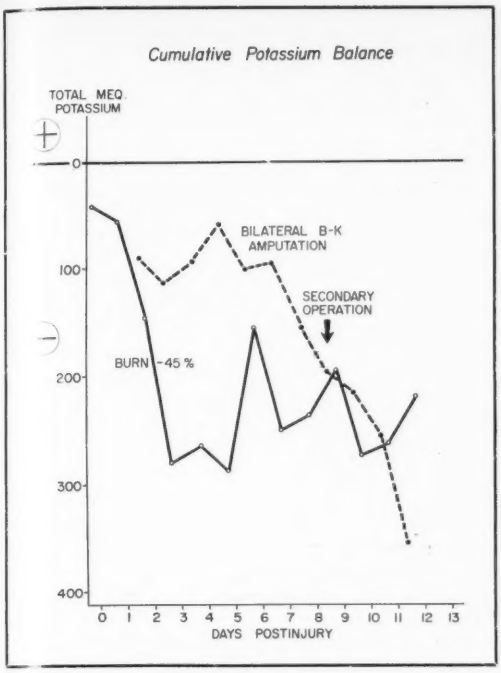

Figure 4. Cumulative potassium balance of the same two patients in Figure 3. The patient with the 45% burn, of which about one-half was third degree, lost considerable quantities of potassium. He had a marked negative cumulative balance for several days. The patient with the amputation had a less severe deficit of potassium which increased after the second operation. These accumulated potassium deficits occurred in spite of potassium therapy. There was no fall in the serum potassium level.

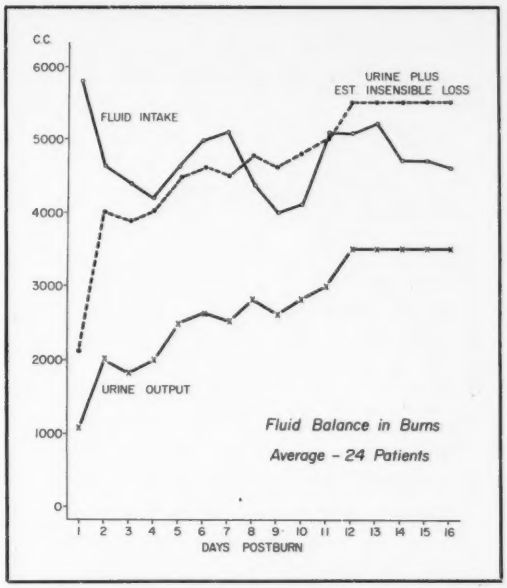

Figure 5. Chart of fluid intake and urinary output in twenty-four burned patients. The average intake and urinary output was computed on twenty-four patients with moderately severe burns. The urinary output rose very slowly over the first twelve-day period. There was no abrupt and sudden diuresis. The dotted line shows the total losses of water when insensible water loss was estimated at two liters a day. The output from urine and insensible loss was about the same as intake by the fourth day. Up until that time there was a considerable positive water balance. After the eleventh day the estimated output exceeded the intake and the expanded interstitial space diminished.

Clinical Implications. Increased amounts of fluid are required soon after trauma for supportive therapy. The plasma volume must be maintained and during this period fluid shifts into the interstitial space. This is more marked in patients with abdominal injuries and burns, than in patients with extremity injuries. Fluid does accumulate around the injured soft tissue wound, as is evidenced by edema. During this initial phase the patient will gain weight. A typical weight curve in a burned patient is shown in Figure 7.[8] After the first week the accumulated water in the interstitial space was excreted, and the patient's weight returned to normal, then due to loss of lean body mass continued to fall. The rapid early weight gain is a reflection in water gain and obscures the fact that the decreases in fat and muscle mass occur simultaneously.

Early after injury fluid must be given, and usually the amount is regulated by urinary output and extra-renal fluid losses. After the first few days a diuresis is expected, and the amount of fluid intake should be determined primarily by extra-renal losses, particularly gastrointestinal losses and insensible water loss. Patients with fevers have an increased insensible water loss and require more water.

Because of the expanding interstitial space sodium must be given to burns and patients with severe injuries. There is a marked increase in the accumulation of sodium in and around the injured area. Little sodium is excreted early, and therefore, the amount of sodium given should be determined by the losses surrounding the injury. Losses from the gastrointestinal tract and into a burn site may be appreciable; where-

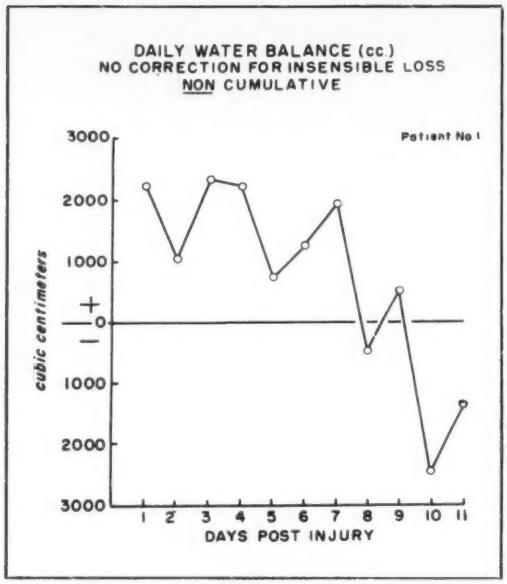

Figure 6. Water balance on a soldier who suffered a traumatic amputation of both legs after a land mine explosion. The intake of water exceeded the urinary output during the first seven days. However, no correction was made for insensible loss. After eight days the urinary output exceeded the intake. This was apparently the period of diuresis. Reprinted with permission of the author[1] and the Annals of Surgery.

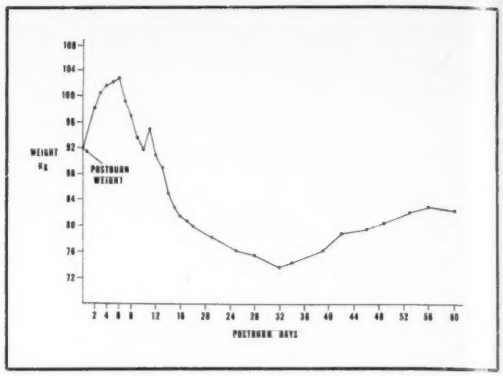

Figure 7. Characteristic weight curve of a severely burned patient. The rapid early weight gain is the reflection of water gain and obscures the fact that decreases in fat and muscle mass occur. Immediately following the maximum weight the early descending limb of the curve usually has a more gentle slope than the ascending limb preceding the maximum. This is due to delay in the excretion of edema fluid. There was a continued loss in weight with loss of nitrogen and fat until the thirty-second day. Thereafter the patient began to store nitrogen and his weight gain increased. However, the fat gain phase did not begin until after the sixtieth day.

as, early losses after uncomplicated surgical procedures are minimal and sodium is contraindicated. Burned patients require little or no sodium after the first 48 hours. In gastrointestinal injuries with gastric suction sodium may be required for several days. The serum sodium changes occurring in 25 patients with severe war wounds are shown in Table 1. In spite of the infusion of one liter of physiologic saline solution daily during the first week the serum sodium remained at low levels. A high percentage of the patients had a serum sodium of less than 130 mEq. per liter.[5] Likewise, in burns the serum sodium will fall to 130 or 135 mEq. per liter in spite of a very positive sodium balance.[6] Unless the concentration of sodium in the serum is abnormally low early after injury, it need not be corrected because a diminished serum sodium is almost invariably associated with a good response. As fluid redistribution occurs after injury, the serum sodium concentration will rise.

Hematocrit determinations after injury in battle casualties are shown in Table 2. Trauma to the extremities is usually followed by a falling hematocrit because of the losses of red cells into the injured soft tis-

HEMATOCRIT DETERMINATIONS IN WAR INJURED.[9]

Average—20 Casualties

TYPE OF INJURY	IMMEDIATELY AFTER INITIAL OPERATION	DAYS POSTOP 1	2	3	4	5	6
ABDOMINAL INJURY	50	52	47.5	48	45	43	44
EXTREMITY INJURY	40.5	38.5	36	32	33	—	—

TABLE 1.

SERUM SODIUM DETERMINATIONS AFTER WAR INJURIES.[5]

Average—25 Battle Casualties

Time	Average Serum Na	Patients With Serum Na Below 130 mEq/L
Before Operation	141	0%
12 Hours Post-Op	141	11%
24 hours	133	45%
2d day	129	45%
3d day	129	44%
4th day	125	46%
5th day	131	25%
6th day	131	46%
7th day	133	20%

TABLE 2.

ses. The losses of cells exceed the losses of plasma. Patients with gastrointestinal injuries usually have a rising hematocrit because the loss of plasma into the intestinal wall and peritoneal cavity is appreciable.[9] The rising hematocrit is associated with the loss of sodium and water into the peritoneal cavity. This phenomenon is somewhat comparable to that seen in burns, namely a rising hematocrit occurs because of a loss of plasma into and around the injured site.

Because of the retention of water and the release of large quantities of potassium into injured cells, there is little need for potassium immediately after injury. As the urinary output increases and renal function is assured, the increased excretion of potassium will lead to a severe negative potassium balance, unless potassium is given. Most injured patients should be given potassium either orally or parenterally beginning 48 hours after injury unless there is interference with renal function.

Nitrogen Metabolism

One gram of nitrogen represents 6.25 grams of protein. An individual lying quietly in bed requires daily about one gram of protein and approximately 30 calories per kilogram of body weight to stay in positive balance. The young healthy adult male in nitrogen equilibrium consumes approximately 60 to 100 grams of protein per day (10 to 15 grams nitrogen) and 2500 to 3000 calories. He excretes about 9 to 12 grams of nitrogen in the urine and 1 to 2 grams of nitrogen in the feces. Following trauma the fecal nitrogen is unchanged, but the urinary nitrogen increases considerably. After severe injuries, particularly in extensive burns, 30 to 40 grams of nitrogen may be excreted a day through the urine.

The chief nitrogen component in the urine is urea; proteinuria is rarely seen in the absence of renal disease. Increased urinary nitrogen excretion begins soon after injury and may continue for very prolonged periods in severe injuries and particularly in burns. During this time the injured patient is in negative nitrogen balance, and there is a gradual depletion of his body protein. Thereafter, as the patient recovers, the urinary nitrogen excretion falls, the patient's intake increases, and nitrogen balance becomes positive. This continues until the body tissues are restored.

The magnitude of urinary nitrogen excretion varies greatly. It cannot be predicted in an individual patient, but a few generalizations seem warranted:

a) There is a rough correlation between the severity of injury and the amount of nitrogen excreted; the more extensive the injury, the larger the nitrogen excretion.

b) Men generally excrete more than women.

c) Usually the urinary nitrogen excretion is less in patients who were malnourished before injury.

In addition to the losses through the urine considerable nitrogen loss may occur by way of the wound exudate. This is particularly common in burns. The amount of nitrogen lost by this route is highly variable but may account for a large fraction of the total nitrogen losses. In a second degree burn, for instance, the nitrogen exudate tends to clines rapidly as the wound heals. In third be high in the early postburn period but dedegree burns with extensive granulating wounds exudate nitrogen is well correlated with the amount of suppuration. The loss of 5 to 7 grams of nitrogen in the exudate

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DERMATOSIS
rapidly spreading
rhus dermatitis
healed within
a week[1]

INFECTED
LACERATION
marked reversal
in 3 days...
returned
to school...
closure advanced[1]

THROMBOPHLEBITIS
back on his feet
in a week after
recurrent episode[1]

REFRACTORY
CELLULITIS
normal routine
resumed after 4 days
of VARIDASE[1]

per day is not uncommon from infected granulating surfaces.

The direct duration and magnitude of negative nitrogen balance are influenced by the nutritional regimen used as well as by the severity of the injury. An energetic nutritional regimen, instituted 7 to 10 days after injury, may reduce substantially the duration of negative nitrogen balance. Unless specific efforts are made to achieve ingestion of a high protein, high caloric diet, negative balance may last for a prolonged period.

Since burns are the most severe form of injury, the magnitude of changes in nitrogen balance are more marked and for longer periods of time than in most other injured patients. Nitrogen balance has been more intensively studied in burns than in other injuries. The cumulative nitrogen balance of a 70% second degree burned patient is shown in Figure 8. This healthy 98 kilogram young male was in negative nitrogen balance in spite of an appreciable intake for 28 days after the burn when cumulative loss of nitrogen was 382 grams and his weight 74 kilograms.[8] As most of the second degree burn healed and the wound closed, he was able to achieve positive nitrogen balance, and therefore many of the cumulative losses were replaced. His cumulative nitrogen balance did not return to zero until the 56th day after injury. At that time he began storing additional nitrogen. His weight had increased but not returned to normal because the fat losses had not been replaced. The last phase in the metabolic response to injury is the so-called "fat-gain phase."[10]

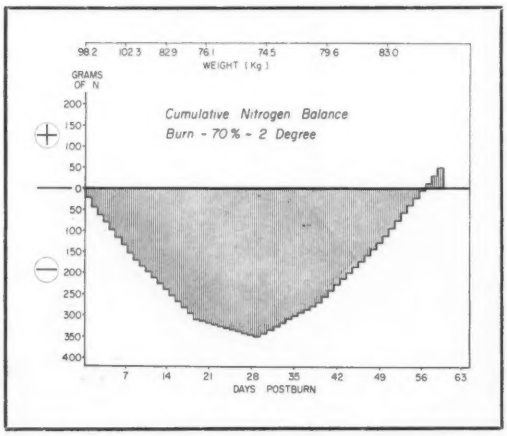

Figure 8. Cumulative nitrogen balance of a patient with a 2nd degree burn of 70% of the body surface. This is the same patient whose weight curve is shown in Figure 7. There was a continuing loss of nitrogen over and above intake for 28 days. During that time the patient lost from 92 to 74 kilograms. Thereafter the balance became positive and the cumulative losses of nitrogen decreased. At the fifty-sixth day the deficit had been replaced and part of the weight loss had been recovered.

The changes in serum proteins following injury are essentially the same as those changes following elective operative procedures, except quantitatively they are more pronounced. Likewise, the changes are even more pronounced in the very severe burn. Following abdominal injury there is a rapid decrease in the albumin-globulin ratio, followed by continued progressive decrease for the next few days. Patients with extremity wounds show a delayed but progressive decrease in albumin-globulin ratio. Electrophoretic studies reveal the changes to involve primarily a decrease in the relative per cent albumin and an increase in the relative per cent of alpha[1] and alpha[2] globulin fractions.[11] Burns of 10 to 15 per cent of the body surface, unless they are very deep, show no marked changed in the level of serum protein, albumin or globulin. In more extensive and deeper burns, however, there are marked changes. Immediately after burning there is a sharp reduction in total serum protein level. This may reflect the expanded interstitial space, which has occurred during fluid and electrolyte administration immediately after the burn injury. From the second to the fifth day the decreased level of albumin is almost wholely responsible for the low total protein. This low level of albumin usually remains for two months or more following the burn. There is an increase in the alpha[2] globulin after burning, but no radical change in beta globulin.[12] The serum gamma globulin during the first six days following the burn suggests only a tendency toward abnormally low levels and not an unequivocal depression. This may be a reflection of increased fluid and electrolyte therapy and expansion of the interstitial space. The initial reduction of gamma globulin is followed by an

increase above the normal range at about the second week following the burn.

The exact role of adrenocortical hormones in nitrogen metabolism after injury is not known. The effect of hydrocortisone-like steroids on nitrogen metabolism is very complex. In general the administration of ACTH, cortisone, and hydrocortisone in large doses induces increased nitrogen excretion. The exact correlation between nitrogen balance and steroid excretion is difficult to interpret. Certain conclusions seem justifiable: (a) severe burns are characterized metabolically by profound alterations in nitrogen balance and steroid metabolism, and (b) since steroids are known to influence protein metabolism, it is quite possible that alterations in nitrogen balance and steroid excretion are related casually.

It appears that the increases in urinary nitrogen excretion soon after injury are directly related to the increase in the secretion of adrenocortical hormones. The marked negative nitrogen balance is also enhanced by the absence of nitrogen intake after injury. Later nitrogen excretion diminishes. This decrease in nitrogen excretion probably reflects a decline in catabolic intracellular protein destruction and indicates that the patient is metabolically prepared to begin anabolic processes and load nitrogen. The storage of nitrogen will not be affected, however, unless adequate amounts of nitrogen and calories are supplied. This can be accomplished by way of diet, or in patients who are unable to take food orally, by parenteral solutions. The storage of nitrogen increases very rapidly after the wound is healed. As nitrogen losses are replaced and the lean body mass increases, then the "fat-gain phase" begins. Body weight increases progressively in the weeks and months that follow if adequate caloric intake is provided.[13] Burned patients will frequently gain from one-half to one pound a day during the first few weeks after discharge from the hospital.

Therapeutic Implications. Immediately after severe injury it is impossible to administer adequate proteins and calories to maintain positive balance. It is not definitely known whether an adequate intake of proteins and calories is absolutely essential. Negative nitrogen balance soon after injury is an acceptable sequel of injury and if it is not prolonged, seems to have little detrimental effect. Prolonged inability to receive proteins and calories, however, will lead to unusual nitrogen losses and severe protein depletion with the attendant predisposition to complications.

Proteins, calories, and vitamins should be given as soon after injury as is practical. In most patients a diet can be started on the second to the fourth day. If this is impossible, the infusion of a protein hydrolysate solution and glucose solutions, along with potassium, should be started. Nitrogen storage will not occur unless adequate potassium is available. Injured patients will usually require 1½ times the normal requirements of proteins and calories. In more severe injuries, particularly burns, larger quantities may be necessary. In children, for instance, about 1½ to 2 times the normal protein and caloric requirements are needed. Male patients show greater metabolic disturbances than females and require 3 to 4 times the normal proteins and twice the normal calories. Female patients can probably be kept in balance with lesser amounts. A good rule of theumb for extensive burns is 2.5 grams of protein and 60 calories per kilogram of body weight per day.[7]

The best type of feeding is a high protein, high vitamin, high caloric diet given three times a day with supplemental protein between-meal feedings. In some instances it is necessary to give supplemental protein by the use of intravenous protein hydrolysate solutions. Protein hydrolysate combined with glucose and alcohol offers 37.5 grams of protein and 800 calories per liter. This solution is a good supplemental protein product, and in patients who are unable to take food by mouth, two liters a day may be very helpful in decreasing the negativity of nitrogen balance. Sometimes when the gastrointestinal tract can tolerate food, but the patient will not eat, tube feedings are beneficial.

There is evidence that testosterone and testosterone-like hormones increase the stor-

age of nitrogen but quantitatively this is not appreciable. Increasing the intake is a better and less expensive method of enhancing nitrogen balance. Androgenic hormones have not been widely accepted for prolonged use to increase the storage of nitrogen.

It is important that an adequate red cell mass be maintained throughout recovery from injury. The hematocrit should be determined periodically and adequate blood given to maintain a hematocrit of 40 to 45.

Carbohydrate Metabolism

There appears to be a decrease in glucose tolerance and some resistance to insulin after injury. These changes reflect an increase in gluconeogenesis and in peripheral carbohydrate breakdown. The increased activity of the adrenal cortex effects carbohydrate metabolism, but this influence is not as clear as the effect of adrenocortical hormones on protein metabolism. After injury the glucose tolerance curve becomes diabetic in type, and the insulin tolerance curve demonstrates a flattening in its pattern. Both the decreased glucose tolerance and the resistance to insulin appear proportional to the degree of injury (Figure 9).[14] These abnormalities diminish as convalescence progresses.

A moderate transient hyperglycemia is a common sequel of burning. This phenomenon is of little clinical importance and usually disappears in several days. A syndrome of so-called "stress diabetes" has been observed a few times in burns.[15] Such patients appear very ill with deficits of salt and water. The phenomenon is usually associated with forced feeding. It would appear that excess carbohydrate intake in patients whose carbohydrate tolerance has been impaired by increased adrenocortical activity gives rise to diabetes. It may be that such patients are borderline diabetics before injury, and that increased adrenocortical stimulation activates a latent diabetic condition.

Fat Metabolism

There is an increased turnover of body fat after injury. A rapid loss of body fat has been demonstrated, presumably due to increased oxidation during the early post-injury period. Extraordinarily large fat losses may occur, particularly after burns. The magnitude of the estimated losses depends upon the severity of the injury. In a severely burned patient the early fat loss may average as much as 600 grams per day. Minimal fat losses have been seen in smaller burns and less severe injuries. The amount of body fat metabolized depends on the nutritional regimen used. An energetic feeding regimen tends to diminish losses. It is doubtful, however, whether any reasonable feeding program can completely prevent them. Fat losses do appear to diminish or almost cease when nitrogen balance becomes positive. After the patient is well into convalescence, he starts into a so-called "fat-gain phase." This phase usually follows repletion of protein deficit, healing of the wounds and ambulation. With a high caloric intake it is sometimes possible to see the deposition of fat, particularly in the face and around the waistline. With additional muscular activity and exercise there occurs a general redistribution of this fat later in convalescence.

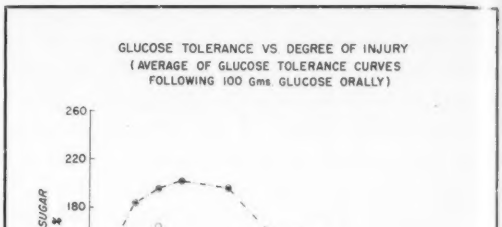

Figure 9. Average glucose tolerance curves in Korean battle casualties with various types of injury. Those casualties with only a minor injury showed an increase in the blood glucose level slightly above controls. Those casualties with major injuries showed a high glucose level that persisted for 90 minutes, followed by a slow fall. It appears that the more severe the injury, the greater the intolerance to glucose. Published with permission of the author[14] and the Annals of Surgery.

Vitamin Metabolism

There is usually a decrease in urinary excretion of thiamine and nicotinamide early after injury. Riboflavin may also be decreased in the urine, but later a brief period of increased excretion of riboflavin is seen. During the convalescent period when the patient is in positive nitrogen balance, there is usually a positive riboflavin balance, when adequate amounts are given. Special emphasis is usually focused on ascorbic acid concentrations. After injury the plasma ascorbic acid concentration diminishes, and its urinary excretion is diminished. The more severe the injury, the greater the disturbance. These changes may continue far into convalescence.[16]

The exact vitamin requirements of the severely injured patient have not been well defined. Since there is evidence of an increased need in vitamins, particularly in burns, the accepted procedure is to give 3 or 4 times the normal requirements of the various components of the vitamin B complex and about 1000 to 1500 mg. of ascorbic acid daily.

Summary

In general, the metabolic response to injury is directly proportional to the magnitude of the trauma. Many of the changes that occur are mediated through the neuroendocrine system. There is an increase in activity of the thyroid and of the adrenal. The 11-oxycorticoids in the urine are increased immediately after injury and may remain increased for several days.

There is diminution in the excretion of sodium and water and in increase in excretion of potassium. Usually there is an expansion of the interstitial space which persists for several days until a diuresis occurs.

One of the most important metabolic changes after injury is the increased outpouring of nitrogen in the urine. This increase in nitrogen excretion may be continued for several days or weeks, depending upon the severity of the injury. As the patient's condition improves, nitrogen losses become less and with adequate intake the nitrogen balance returns toward normal. Later, as the patient's wound heals, there may be considerable storage of nitrogen.

There is a decrease in glucose tolerance after injury, which usually disappears after a few days, unless the injury is massive or there is continuing stimulation.

A rapid loss of body fat occurs during the early postinjury period. These fat losses may continue for a prolonged period. They diminish when nitrogen balance becomes positive. Later in convalescence, if the patient is on adequate intake, an appreciable gain in fat is seen.

These changes in metabolism give an indication of the type of supportive therapy required after injury.

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DISCUSSION

DOCTOR FURMAN, Associate Professor of Research Medicine, University of Oklahoma School of Medicine: Doctor Artz, do you use an anti-catabolic agent such as testosterone? If so, when would you recommend their use, initially, or during the later stages when the big deficit has to be made up?

DOCTOR ARTZ: There is no doubt that these agents enhance the storage of nitrogen as shown by Doctor Abbott's studies. Our own studies showed that they did not continue to enhance the storage of nitrogen over long periods of time and therefore I don't use them. In general, what we try to do is to do as Doctor Abbott has pointed out and try to obtain an adequate intake of nitrogen and calories. Little else is done to disturb the homeostatic mechanisms of the patient other than closing the wound.

DOCTOR ABBOTT: We feel that in most of the patients, forcing food and giving anabolic hormones are probably not necessary. However, I think in the older individual who falls and breaks a hip, very often an injection of testosterone propionate with or without estrogen may be helpful. Certainly, such therapy is often accompanied by a feeling of well-being. In our experience, such patients have shown a better utilization of nitrogen for 12 or 15 days, and we have not felt that it was necessary to do further balance studies because these patients were then usually eating well and over their troubles. In these patients, we have noted a renewed interest in life in many of the old people, and often their caloric intake will also improve. I certainly feel that it is a much better stimulating agent than any of the adrenal steroids. The latter agents are catabolic in effect and the testosterone compounds are therefore preferable to adrenal hormones for such patients.

Clinical Aspects of Magnesium Metabolism

JAMES F. HAMMARSTEN
WILLIAM O. SMITH

KNOWLEDGE OF THE ROLE of magnesium in human physiology is incomplete, but several vital functions of this ion have been established. Many of the intracellular enzymatic reactions in the intermediary metabolism of glucose depend upon magnesium as a co-factor, examples of which are the conversion of glucose-1-phosphate to glucose-6-phosphate and the decarboxylation of pyruvic acid.[1] The extracellular concentration of magnesium may be of considerable importance in muscle function. Magnesium has a sedative action at the neuromuscular junction by a blocking of acetylcholine release, which effect is antagnoized by calcium.[2]

The normal adult human body contains about 20 gms. of magnesium, 98% of which is within soft tissue cells and bone.[3] Striated muscle contains as much as 20 mEq/liter of magnesium. The serum magnesium level is variously reported in the literature from 1.21-2.45 mEq/L. (range of means), depending on the individual laboratories and the method employed. Obviously each laboratory must establish its own normal values for serum magnesium. Spinal fluid magnesium is generally slightly higher than in serum.[4] Gastric juice appears to contain about 1.0 mEq/L. of magnesium.[5] Magnesium concentration in bile approximates that of the blood serum.

The daily requirement for magnesium is about 5 mg./Kg. of body weight. The average-size person can remain in balance on 220 mg. daily.[6] Magnesium is provided in the diet largely by leafy green vegetables, meat, and milk. Absorption from the intestine is probably regulated by the same factors that govern calcium absorption. The great majority of ingested magnesium is ordinarily excreted in the feces; only a small percentage is recoverable in the urine. Renal tubular reabsorption of magnesium occurs to a high degree, probably approaching that of calcium. Whether the tubules can also excrete the cation has not yet been

established, despite several attempts to solve this question.[7,8] As with calcium, there appears to be secretion of magnesium into digestive juices forming a "gut pool," and the small bowel contents seem to be rather rich in magneisum.

The controlling mechanisms for the usual serum cations have been demonstrated, but little is known concerning the regulators of magnesium metabolism. Recent evidence strongly suggests that the parathyroid gland is instrumental in this regard.[9]

A portion of the serum magnesium is bound to serum proteins. This appears to be about 20-30% as compared to 50% for calcium.[10] Evidence is accumulating that there is competition between calcium and magnesium for binding by the protein moieties.[11]

Twenty-six years ago, Kruse, Orent and McCollum showed that rats deprived of dietary magnesium manifested hyper-irritability followed by convulsions and death.[12] Concurrently other workers established that "grass staggers" in cattle was due to magnesium deficiency.[13] Two years later Hirschfelder reported a group of patients with low serum magnesium and symptoms of twitching and convulsions. These patients had renal disease or epilepsy. Several case reports also appeared in the literature linking hypomagnesemia to tetany in patients with severe diarrhea.[15] However, since some observers noted low serum magnesium values in patients without symptoms, symptomatic magnesium deficiency in man was not universally accepted.

Six years ago, Flink and associates reported a well-documented series of patients with delirium tremens who showed low serum concentrations of magnesium.[16] Following intramuscular magnesium sulfate therapy, the symptoms of tremor and hallucinations cleared rapidly with a concurrent rise in serum magnesium. These observers also reported twitching, athetoid movements, and hallucinations associated with a low serum magnesium in patients with massive fluid loss, receiving no magnesium in the replacement solutions. These observations have been amply confirmed.[17,18,19] McCollister, Flink and Doe have recently reported evidence for total body depletion of magnesium in patients with delirium tremens.[20]

The magnesium deficiency syndrome has also been observed in patients with chronic renal disease prior to the development of azotemia,[21] patients with osteolytic disease and hypercalcemia,[22] patients with hypoparathyroidism,[9] and patients undergoing marked diuresis induced by mercurial diuretics.[23] Hypomagnesemia has been reported in some cases of idiopathic epilepsy. The results in a variety of disorders are summarized in figure 1 and table 1.[19]

STATISTICAL ANALYSIS OF SERUM MAGNESIUM IN VARIOUS CLINICAL DISORDERS

	No.	Mean (meq./L.)	S. D.	P
Normals	40	1.48	±0.17	
Delirium Tremens	12	1.14	±0.38	<.001
Portal Cirrhosis	17	1.48	±0.19	
Diabetes Mellitus	39	1.57	±0.13	<.02
Insulin Coma	17	1.70	±0.08	<.001
Renal Disease				
Not Azotemic	11	1.33	±0.36	>.05
Uremia—				
No CNS Depression	12	1.68	±0.35	<.02
Uremia—				
CNS Depression	9	2.49	±0.60	<.001

Table 1

Serum magnesium values in the 12 patients with delirum tremens are shown in figure 1. The mean value is 1.14 ± 0.38 mEq/L., a highly significant decrease as compared to the normals ($P < .001$) (Table 1). However, it may be seen that only five of the group were completely below the normal range and seven were less than 1 S. D. below the normal mean. All of the patients showed marked improvement with magnesium administration.

A patient with ulcerative colitis having severe diarrhea, no oral intake, and intravenous fluid replacement containing no magnesium has been reported previously.[3] The serum magnesium in this case fell to 0.70 mEq/L. and the patient showed the characteristic clinical picture of magnesium deficiency, which improved dramatically with parenteral magnesium administration (Figure 2).

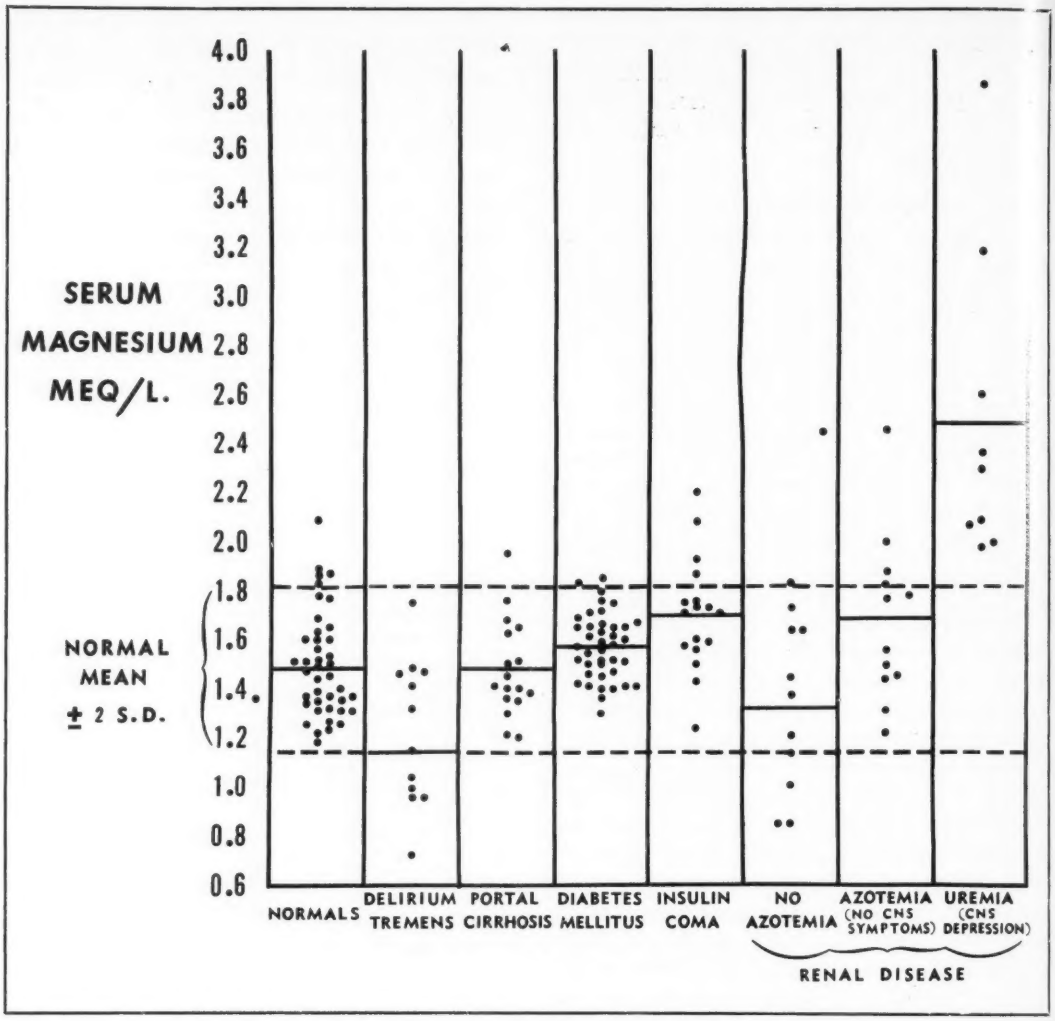

Figure 1. Serum Magnesium in Normals and Various Clinical Disorders.

Treatment of magnesium deficiency at present consists of parenteral replacement with magnesium sulfate. We feel that absorption of magnesium sulfate given orally is inadequate for replacement. The intramuscular route is commonly used and initially 8.0 gms. are given daily in four divided doses. After 48 hours, the dosage may be decreased to 4.0 gms. daily. Obviously, therapy must be given until the deficiency is corrected and maintenance levels must be provided if loss continues. The therapy should not be used in anuric patients and with great caution in oliguria or uremia. We feel it would be wise to add magnesium sulfate to sustaining fluid solutions in patients with deficient oral intake. Daily requirement could be met by 1.0 gm. daily.

Deleterious effects of excessive magnesium have been reported in only one circumstance, uremia. Hirshfelder reported several cases of coma and death in patients with uremia given frequent doses of magnesium sulfate as a cathartic.[14] We have noted high serum magnesium levels in patients with chronic renal disease, nitrogen retention, and central nervous system depression without magnesium administration (Figure 3).[21] Large doses of magnesium in animals pro-

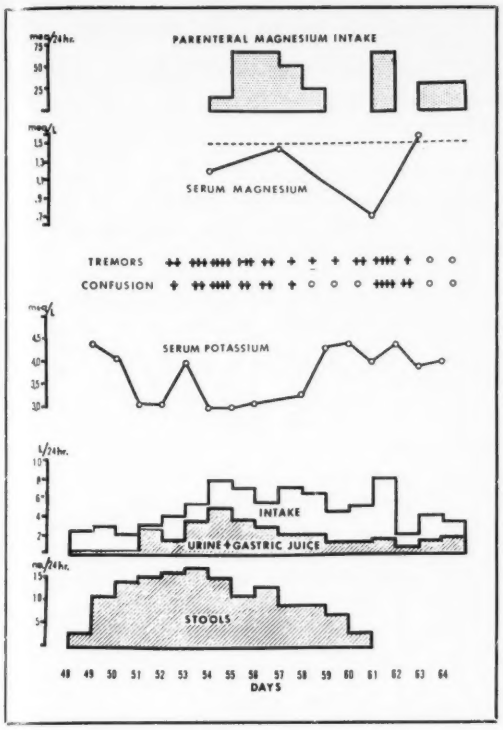

Figure 2.

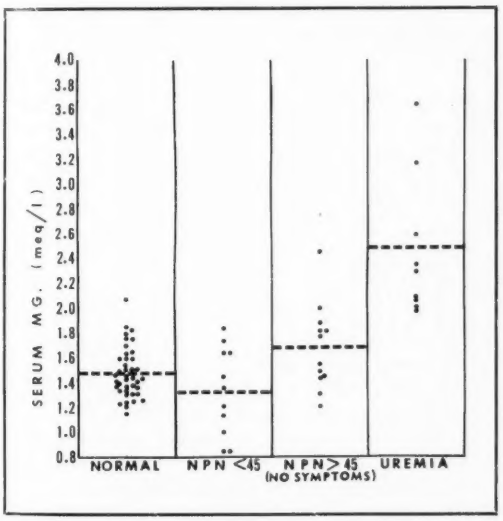

Figure 3. Individual Serum Magnesium Values in Normals and in Patients With Renal Disease.

duces central nervous system depression with coma and death. Our data suggest the possibility that the central nervous system depression and coma in uremic patients may be related to high serum magnesium values. However, some patients with renal disease without azotemia have quite low values and may develop symptoms of magnesium deficiency. The mechanism leading to this hypomagnesemia is not yet established, but appears to be on the basis of an increased urinary loss. Similar findings have also been reported recently in patients with acute renal failure.[24]

Since magnesium is predominately an intracellular ion, we have recently determined the red cell magnesium concentration in normals and patients with delirium tremens and uremia.[25] The values in these groups are given in Table 2. While the evidence is only

	No.	Erythrocyte Red Cell Mg.
Normal	13	5.29± .34 mEq/L.
Delerium Tremens	4	2.30± .70 mEq/L.
Uremia	6	8.91± 1.48 mEq/L.

Table 2.

preliminary, it appears that states associated with a low or high serum value are associated with a corresponding change in the red cell magnesium.

In summary, magnesium is important in biochemical functions of man. A body deficit of magnesium produces a clinical syndrome of mental clouding, confusion, disorientation, hallucinations, tremor, athetoid movements and occasionally actual convulsions. Deep tendon reflexes are generally hyperactive and a cardiac arrhythmia (ventricular irritability) has been noted. This syndrome has not been observed in delirium tremens, massive fluid loss, chronic renal disease prior to the development of azotemia, hypercalcemia, and hypoparathyroidism. Treatment consists of parenteral magnesium replacement. Hypermagnesemia has been observed in patients with uremia, where it is believed to have a role in the central nervous system depression. Artificial dialysis may be indicated when hypermagnesemia is noted in patients with reversible kidney lesions.

It appears that with the development of better methods of determination and an increased awareness on the part of physicians in regard to this cation, magnesium will take its place beside sodium and potassium in clinical medicine.

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DISCUSSION

DOCTOR CONRAD: Doctor Hammarsten, we hav two questions for you from one of your fellow pan members.

First, Doctor Relman wants to know, do you thi that the increased plasma magnesium in uremia cou teracts the neuromuscular effects of the lowered ca cium which often occurs?

DOCTOR HAMMARSTEN: I think it is entire possible. It is well known that there is an antagonis between the two, so that, for instance, it is possib in a normal individual to infuse magnesium and pr duce hyporeflexia and then correct this by giving the patient calcium. I think Doctor Relman's idea is entirely possible.

DOCTOR CONRAD: And his second question is with reference to one of the slides you showed. He wants to know why the control clearance of magnesium is higher in uremics than in normal individuals.

DOCTOR HAMMARSTEN: The difference was not significant, actually.

DOCTOR RELMAN: Were these subjects with high initial serum magnesium levels?

DOCTOR HAMMARSTEN: They were people who had a slightly high initial magnesium, yes.

DOCTOR CONRAD: In the past, magnesium sulfate has been given to patients with toxemia of pregnancy. Are there any studies of magnesium values in these patients; and secondly, would you consider this therapy contraindicated if these patients were also uremic?

DOCTOR HAMMARSTEN: There have been some studies, but we haven't done any. The studies[1,2] that have been done have shown a normal magnesium. I believe that I would hesitate to use magnesium in patients who were uremic, although I have not had any personal experience with the particular problem. I might mention that the amounts of magnesium sulfates that are used are tremendous compared with what is necessary to replace the usual deficit, and these patients oftentimes get extremely high serum magnesiums.

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Magnesium and Calcium Interrelationships

LEONARD P. ELIEL
WILLIAM O. SMITH
CARL THOMSEN

A. Introduction

MAGNESIUM AND CALCIUM share common chemical and physiologic properties. They are divalent metals of the alkali-earth group, one being subjacent to the other in the periodic table. Their concentrations in body fluids are of critical importance to neuromuscular function, plasma deficits being associated with increased irritability, convulsions and tetany, and plasma excess with decreased irritability, weakness, and paresis. Possible metabolic interrelationships between the two metals have excited sporadic interest for some time. Mendel and Benedict in 1909,[1] and others[2,3] have investigated the effects of oral and perenteral calcium or phosphate loads on the serum concentration and excretion of magnesium in animals. Parenteral injection of calcium in the rat resulted in increased urinary excretion of magnesium[1] while oral and parenteral calcium or phosphate loads in the dog resulted in falls in the blood magnesium levels.[2,3]

In 1933, Bulger and Gausmann reported loss of magnesium (as well as of calcium) in hyperparathyroidism and retention during post-operative recovery[4] (see also references [5,6,7]). Others have reported parallel changes in the urinary calcium and magnesium of patients under androgenic treatment for breast cancer.[8]

These observations suggest that the metabolism of calcium and magnesium are interrelated. We have explored the nature of this interrelationship in osteolytic disease, after calcium and phosphate loads, and after administration of various endocrine and pharmacologic agents.

B. Magnesium Deficit in Osteolytic Disease

Our interest in this field was aroused by the observation of a small group of patients with neoplastic osteolytic disease who developed symptoms of magnesium deficiency in association with hypercalciuria, hypercalmemia, and hypomagnesemia.[9,10] The symptoms were characterized by tremors, athetoid movements, convulsions (in the absence of demonstrable central nervous system metastases, in life or at post-mortem) and, occasionally, by hallucinations, hypertension, and electro-cardiographic disturbances. All manifestations were abolished by the parenteral administration of magnesium sulfate. The data from three of these patients, prior to therapy, are summarized in Table I.

Metabolic studies on these three patients revealed that there was invariably a striking correlation between peaks of urinary

		Diagnosis	Calcium meq/L	Serum Magnesium meq/L	Clinical Findings
1.	M.W.	Carcinoma of breast	8.0	1.0	Clonic convulsions Hypertension Hyperactive reflexes Cardiac arrhythmia
2.	V.A.	Carcinoma of breast	8.5	0.9	Colonic convulsions Hypertension Hyperactive reflexes
3.	C.E.	Multiple myeloma	7.5	1.1	Tremor of Arms Athetoid movements
		Normal	4.5-5.5	1.6± .22 (S.D.)	

TABLE I

calcium and magnesium excretion. An example of these data (from patient 1, Table I) is illustrated in Figure 1.

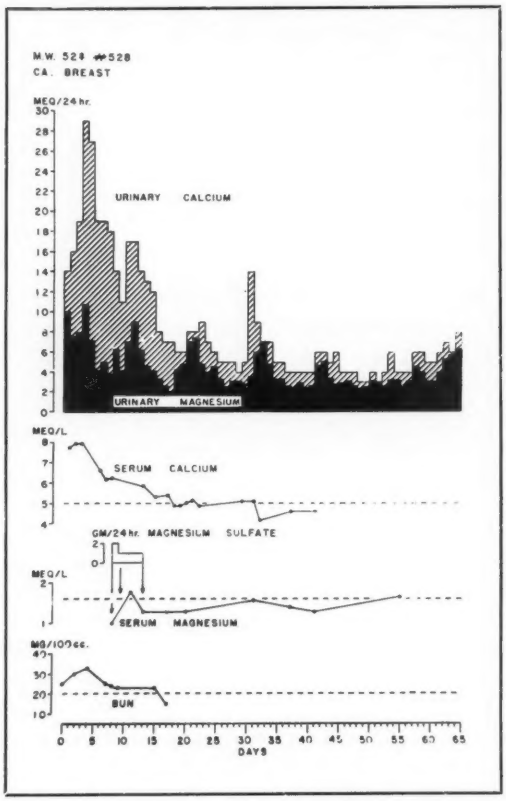

Figure 1. Serum calcium, magnesium, and BUN; and daily urinary calcium and magnesium excretion in case 1 (M.W.), Table I.

Substantially more magnesium appeared in the urine (on reasonably constant magnesium intakes) than would be anticipated on the basis of bone destruction, and the usual ratio of magnesium to calcium in bone which is 1 meq/40 meq.* These data are illustrated in Table II (also from patient 1).

Period	Days	Predicated magnesium loss based on Mg/Ca in bone meq/Period	Actual Mg Loss meq/Period
1	5	-.15	-4.9
2	3	-.07	-5.4
3	7	-.25	-4.2
4	4	-.05	-2.6

TABLE II

*Based on analyses in our laboratory of non-pathological, human cortical bone.

The urinary losses were not accounted for on the basis of extra-cellular fluid depletion.

We assumed, then, that hypercalciuria is associated with urinary magnesium loss and that this leads to an extra-cellular deficit and to depletion of magnesium from another locus which may be intra-cellular or which may represent a preferential withdrawal from bone crystal surfaces (see below). The magnesium depletion, it is further assumed, leads to the production of clinical symptoms.

Since these observations were made, we have examined the nature and pathogenesis of magnesium deficit associated with hypercalciuria and have arrived at a tentative explanation for its occurrence, through the studies now to be described.

1. *Renal Damage.* Renal damage and uremia supervene ultimately in patients with hypercalciuria. Could this be responsible for magnesium loss? While the patients described in Table I had abnormal elevations of the blood urea nitrogen level, we have observed magnesium loss in hypercalciuric patients with normal renal function, determined by the usual clinical criteria. As will be noted below, magnesium loss is also observed in patients with induced hyperparathyroidism and hypercalciuria who have no evidence of renal impairment. We have, therefore, excluded clinically demonstrable renal impairment as a cause of the magnesium deficit.

2. *Hypercalciuria and Hyperphosphaturia.* Patients with destructive bone lesions excrete excessive quantities of calcium and phosphate in the urine. We have, therefore, administered large loads of calcium and phosphate intravenously in an effort to induce magnesium loss.

Intravenous loads of calcium gluconate (up to 50 meq Ca in 4 hours) equivalent to 1000 mg Ca) have been administered to two patients with normal bones and two patients with osteolytic disease (multiple myeloma, and breast cancer) under metabolic balance conditions. All patients had normal renal function. The results in all four cases were similar. Hypercalciuria of 600 mg/day and hypercalcemia of 16 mg% were induced in a typical example (figure 2). The serum

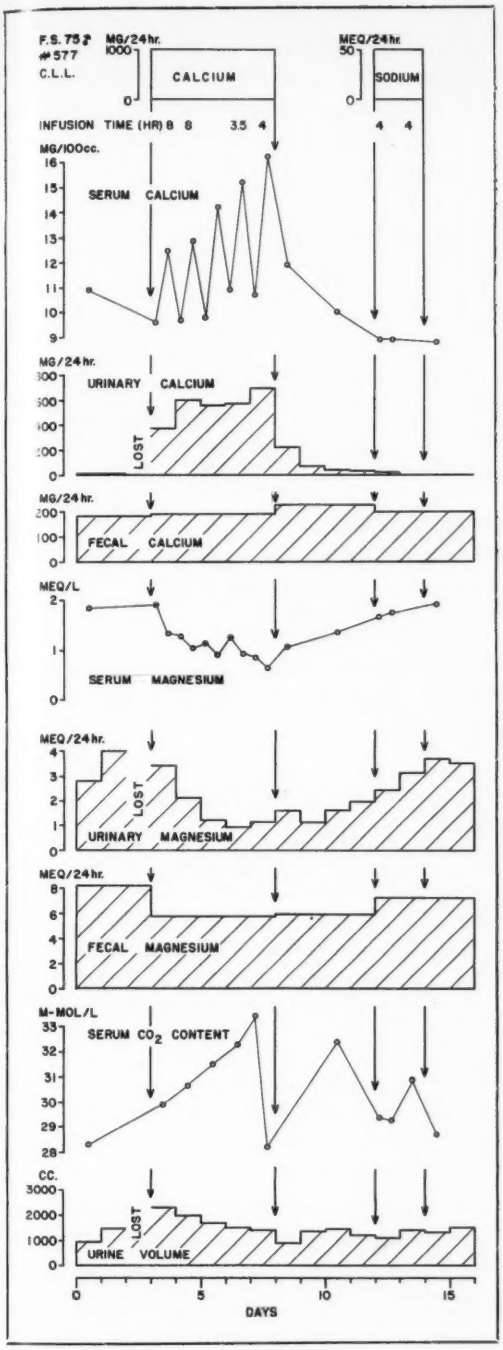

Figure 2. The effects of loads of calcium gluconate and of sodium lactate on the serum concentrations of calcium, magnesium and CO_2; and on the urinary and fecal excretions of calcium and magnesium in a man without osteolytic disease.

magnesium fell from 2.0 meq/L to 0.7 meq/L, but the urine magnesium excretion dropped to 25% of control levels. Infusion of an equivalent amount of cation as sodium lactate failed to reproduce these changes. The balance data revealed addition of magnesium to a body compartment, which we must assume was either bone or intra-cellular, non-osseous tissue. "Intra-cellular" magnesium balance data for a five day loading period, in the example cited, resulted in a retention of 35.2 meq, rather than a loss. We concluded that excess urinary calcium *per se* does not engender magnesium loss.

Intravenous loads of buffered sodium phosphate, providing up to 60 meq of phosphate in a four-hour period, produced no change in the magnesium balance in two patients. As with calcium loading, however, the serum magnesium tended to fall, though not so strikingly (figure 3). We concluded that excess urinary phosphate *per se* does not lead to magnesium loss.

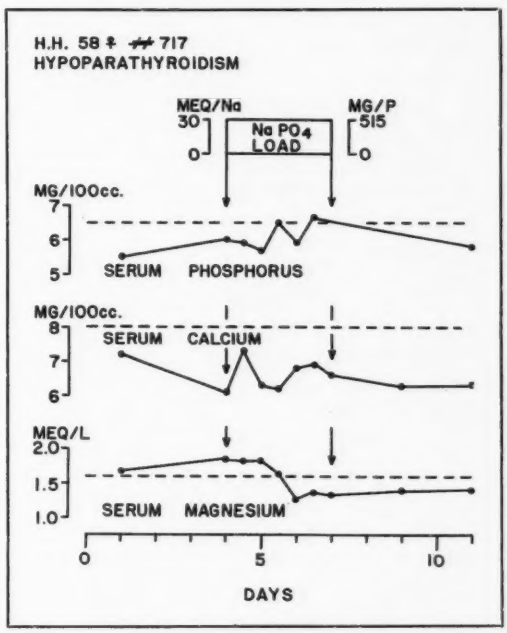

Figure 3. The effect of a buffered sodium phosphate load on the serum concentrations of calcium, magnesium, and phosphorus in a patient with hypoparathyroidism.

3. *Studies in Patients with Hypoparathyroidism.* Patients with hypoparathyroidism afford ideal subjects for the study of wide variations in urine calcium and serum calcium concentrations, in relation to magnesium.

Six patients with hypoparathyroidism (two idiopathic, four post-operative) have been studied. Both cases of idiopathic, and two cases of post-operative, hypoparathyroidism demonstrated serum magnesium levels slightly but significantly below normal (1.2 to 1.3 meq/L—normal mean: 1.6 meq/L), in association with hypocalcemia and hyperphosphatemia.

Administration of parathyroid extract to three patients, maintained on constant diets, resulted in almost exactly parallel changes in urinary calcium and magnesium, from an initial drop over the first two days to subsequent rises above control levels. A typical example is illustrated in figure 4. The serum magnesium, low in two of the patients, likewise paralleled in striking fashion the rise in serum calcium, associated with administration of the extract, and paralleled also the fall after its withdrawal (figure).

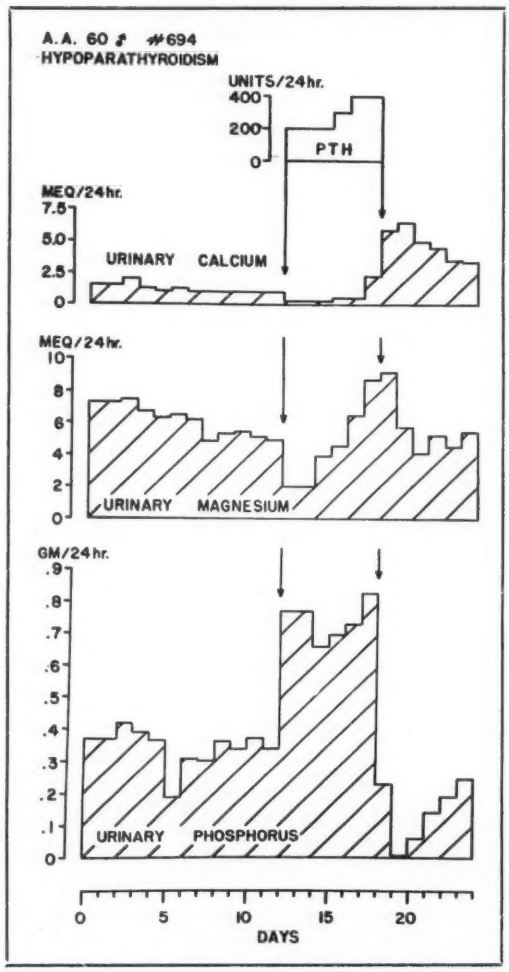

Figure 4. The effects of parathyroid extract on the daily urinary excretion of calcium, magnesium, and phosphorus in a patient with idiopathic hypoparathyroidism on constant dietary intake.

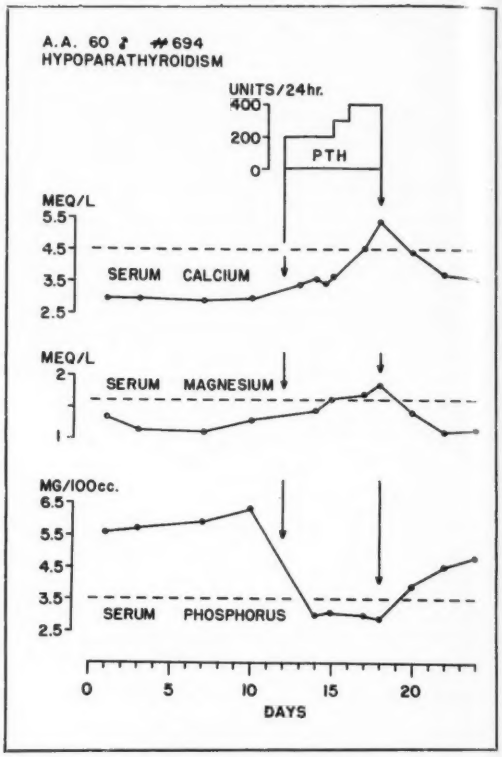

Figure 5. The effect of parathyroid extract on the serum concentrations of calcium, magnesium, and phosphorus in a patient with idiopathic hypoparathyroidism.

Similar observations have been made in one hypoparathyroid patient who received dihydrotachysterol (AT 10) and another who received vitamin D.

It appears from these observations that parathyroid extract and pharmacologically related substances have similar effects on the metabolism of both calcium and magnesium. This is not surprising in view of the close chemical relationship between these two members of the alkali-earth group.

The magnesium balances, obtained from the hypoparathyroid patients receiving parathyroid extract, dihydrotachysterol (AT 10) or vitamin D, were all negative even after correction for losses which might be

attributed to changes in the volume or mass of bone, soft tissue, or extra-cellular fluid. These corrected balances are summarized in the following table:

Patient	Rx	Dose per day	Duration days	Corrected Mg Balance, meq/period
	Control	—	6	— 0.3
	PTE*	200-400 u	6	—14.2
	Control	—	5	+ 3.4
	PTE*	400 u	6	—17.3
	Control	—	5	+ 9.4
	AT 10 #	6.25 mg	7	— 8.6
	Control	—	7	+11.6
	Vit. D	400,000 u	7	—17.5

* PTE = parathyroid extract

\# AT 10 = dihydrotachysterol

TABLE III

Thus, administration of parathyroid extract, or large doses of AT 10 or vitamin D, is associated, like malignant osseous disease, with depletion of body magnesium. (None of the patients under investigation had renal impairment.)

Hyperparathyroidism due to parathyroid adenoma appears also to be associated with magnesium deficit. It has been noted by several observers that there is retention of magnesium following removal of the adenoma.[4,5,6,7] Barnes and his co-workers[6] calculated that the retention is greater than that which can be accounted for on the basis of deposition of magnesium in bone, suggesting antecedent deficit. Hyperparathyroidism may be associated preoperatively with extra-cellular deficit (hypomagnesemia);[6,11] or with falling serum magnesium levels after removal of the adenoma,[7] presumably due to repair of the deficit at the expense of extracellular magnesium.

Since administration of substantial doses of parathyroid extract results in tissue magnesium deficit (see Table III), these observations in hyperparathyroidism are expected. It is surprising, though, that serum magnesium concentrations should be low in both hypo- and hyperparathyroidism. While hypomagnesemia in the latter instance seems easily explained on the basis of renal magnesium loss, we believe the former may be ascribed to physical-chemical phenomena (see below).

4. *Intra-cellular Phosphate Depletion.* The large phosphuresis induced by administration of parathyroid extract (see figure 4), and large doses of AT 10 or vitamin D, represents an intra-cellular depletion of phosphate, since it is not accompanied by nitrogen, nor initially by calcium. Is there a requirement for excretion of intra-cellular cation, with phosphate, which is satisfied by magnesium? Actually during the initial phases of therapy only about 10% of the cation required to cover phosphate is met by magnesium, the remainder being made up from sodium, potassium, ammonia and titratable acid.

We have further tested the possibility that intra-cellular phosphate loss requires concomitant magnesium excretion, by the administration, to a patient with hypoparathyroidism, of acetazolamide (Diamox), an agent which induces phosphuresis, in doses of 1000 mg/day for four days. Phosphate excretion doubled, without increase in either nitrogen or calcium excretion, representing, therefore, intra-cellular phosphate depletion. No magnesium loss resulted, however. This experiment has also been confirmed in a normal subject. We have concluded that intra-cellular phosphate depletion does not lead to magnesium deficit.

5. *Citrate Metabolism and Magnesium Deficit.* We were prompted then to seek a factor common to patients with malignant osteolytic disease, and to patients with hyperparathyroid states, which would account for the preferential extraction and excretion of magnesium. An exact parallelism between urinary citrate and calcium excretion was described by Shorr in 1942,[12] a relationship which held whether variations in urine calcium were the result of dietary alterations or of changes in the rate of resorption of calcium from bone. The possibility that citrate could be involved in the production of the magnesium deficit associated with hypercalciuria was rendered more attractive by the demonstration of Hastings, and co-workers, in 1934, that citrate complexes both Ca^{++} and Mg^{++} and that at pH 7 both complexes act as weak electrolytes with dis-

sociation constants of pK's which are practically identical, 3.22.[13]

Under normal conditions of calcium, magnesium and citrate excretion, citrate is theoretically capable of complexing up to ⅔rds of urinary calcium plus magnesium. It is reasonable to postulate that variations in citrate production and/or excretion might result in parallel excretory changes, therefore, in both calcium and magnesium. If citrate binds Mg^{++} as avidly as Ca^{++}, and if magnesium is more readily available for complexing at the surface of the crystal lattice*, then we have a logical explanation for the appearance of more magnesium in the urine than we could anticipate from its very low ratio to calcium in bone. It has already been demonstrated that blood and urine citrate increase following administration of parathyroid extract and vitamin D.[14,15]

Large variations in citrate excretion were induced in a patient with hypoparathyroidism to test this possibility. Hypercalciuria and mild hypercalcemia were first induced with parathyroid extract. During administration of the extract, hydrocortisone was exhibited in doses of 100 mg/day for 6 days and then discontinued,** while the extract was continued for another 4 days. The urinary citrate excretions and corresponding magnesium balances are shown in the following table:

Period	Days	Citrate mg/24 hr	Mg balance meq/24 hr
Control	12	656	+5.0
PTE	8	890	—1.3
PTE + F #	6	288	+0.8
PTE	4	1080	—3.6
Control	4	630	+4.9

TABLE IV

There is an excellent correlation between increases in citrate excretion and the production of a negative magnesium balance, suggesting that changes in citrate production and excretion can account for the development of magnesium deficit.

The hypothesis that increased citrate production in osteolytic disease accounts for the magnesium deficit would make reasonable the assumption that magnesium is lost from bone rather than from soft tissue. Magnesium is firmly bound in soft tissues and is even difficult to extract *in vitro*.[7] The further assumption might be made that the Mg-depleted crystal surface would avidly repair its deficit at the expense of extra-cellular fluid magnesium, given normal citrate production. This appears to be the case in patients with hyperparathyroidism who, following successful removal of an adenoma, manifest symptoms of magnesium deficiency in association with hypomagnesemia and normal serum calcium levels.[6,7]

6. *The Relationship Between the Concentrations of Ca, Mg and P in Serum.* Analysis of all of our data from patients with malignant osteolytic disease, from hypoparathyroid patients, before and after treatment, and from loading studies, reveals that the relationship between the serum concentrations of Ca, Mg, and P is best expressed by an empirical formula $(Ca^{++} + Mg^{++}) \times (P) = 16 \pm 2$ (S.D.) (expressed in milli-equivalents, with an assigned valence of 1.8 to phosphorus). Thus, in the presence of hyperphosphatemia (as in hypoparathyroidism or phospate loading) both Ca^{++} and Mg^{++} tend to be low, while in the presence of hypercalcemia and normal phosprorus concentrations (as in osteolytic disease without renal impairment, or calcium loading), the serum magnesium concentration tends to be low. In hyperparathyroidism with hypercalcemia and hypophosphatemia, we have observed normal serum magnesium concentrations but low values have been reported in patients with parathyroid adenoma.[11] It appears then that the serum magnesium concentration shares in the same physical-chemical mechanism that regulates the calcium and phosphorus concentrations.

C. Vitamin D and Intestinal Absorption of Magnesium

Since vitamin D increases intestinal absorption of calcium, its effects on the absorption of magnesium were tested at a dose

*Magnesium may be held to the surface of the crystal lattice by electrostatic attraction rather than being an integral part of the crystal structure.

**Henneman et al.[16] and Mueller, et al.[17] have shown that cortical steroids depress citrate levels in blood and urine.

#Hydrocortisone (cortisol).

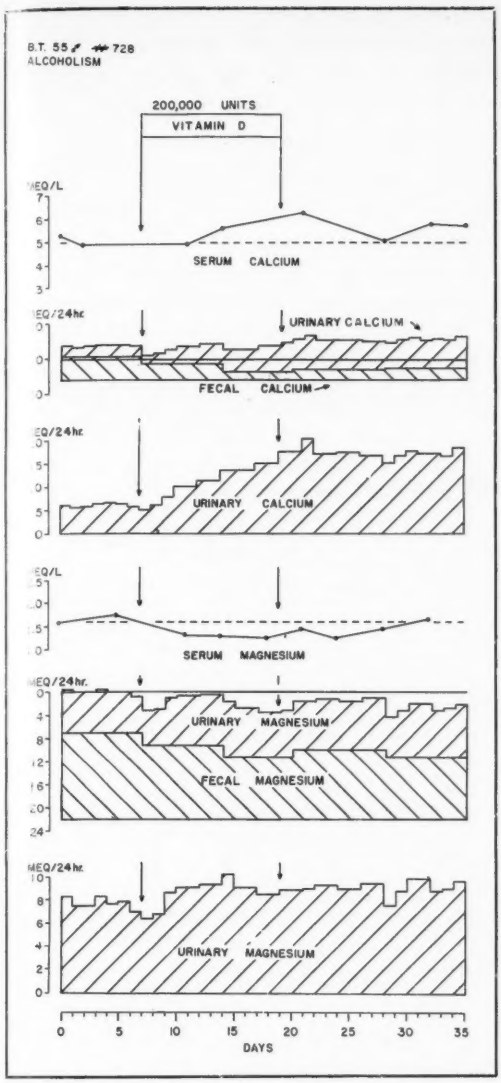

Figure 6. The effect of Vitamin D on the serum concentrations of calcium and magnesium and on the daily urinary excretion of calcium and magnesium in a patient with normal parathyroid function maintained on a constant dietary intake.

The calcium and magnesium balances are plotted in the conventional fashion, the baseline representing intake, a clear space below the zero line representing positive balance, and excretions rising above the zero line, a negative balance.

of 200,000 units per day in a patient with normal parathyroid function. The usual effects on calcium excretion were noted (figure 6), that is, a marked decrease in fecal excretion and a rise in urinary excretion, indicating increased intestinal absorption. Similar, though less marked, changes were noted in the magnesium content of the urine and feces, suggesting that vitamin D does, to a certain degree (at least in the patient studied), increase intestinal absorption of this ion. The balance of magnesium became positive during the period of vitamin administration and remained positive for at least 16 days after it was stopped. The retention of magnesium is greater than can be accounted for on the basis of bone formation and must represent increase in extraosseous tissue magnesium or deposition of magnesium on the bone crystal surface. It is noteworthy that the serum magnesium concentration fell, while that of calcium rose during the period of vitamin ingestion. The storage of magnesium in this patient, in contrast to the loss observed in patient 4 (Table III), may be attributed to the lower dose of vitamin D employed.

D. The Relationship of Serum Magnesium Levels to Tetany

One might suspect that the plasma magnesium concentration could influence the appearance and degree of hypocalcemic tetany. Magnesium sulfate, 5 gm., was infused intravenously into a hypoparathyroid patient (patient 3, Table III), prior to replacement therapy, over a four-hour period, raising the serum magnesium to 3.58 meq/l. During and following the infusion there was virtually complete disapparence of marked Chvostek and Trousseau signs, though the serum calcium concentration remained low. Hammarsten and co-workers (see elsewhere in this symposium) have shown that many patients with uremia exhibit elevated plasma and erythrocyte magnesium levels. This fact may account for the absence of tetany in uremic patients with hypocalcemia resulting from renal failure and hyperphosphatemia. Conversely, one would anticipate that low plasma magnesium levels would facilitate the appearance and augment symptoms of tetany, since convulsive manifestations were observed even in patients with somewhat elevated serum calcium concentrations (Table I).

Summary and Conclusions

1. Destruction of bone due to neoplastic disease may be associated with increased

urinary excretion of calcium, phosphorus, and magnesium; occasionally, hypomagnesemia and symptoms of magnesium deficiency, i.e., tremors, athetoid movements, convulsions, hallucinations, hypertension, and cardiac arrhythmias are observed. Parenteral administration of magnesium sulfate relieves these symptoms promptly. We have attempted to locate the source of magnesium depletion and to study possible factors governing or contributing to the magnesium loss.

2. The loss of magnesium associated with the hypercalciuria is in marked excess of that which one would anticipate from depletion of extra-cellular fluid and loss of bone minerals, indicating either a soft-tissue deficit of magnesium or preferential extraction of magnesium from bone.

3. Impaired renal function, or a renal lesion, can probably be excluded as a cause of the magnesium loss.

4. Exogenous loads of calcium or phosphate, given intravenously, fail to induce urinary magnesium loss but result in falls in the serum magnesium concentration and tissue magnesium storage.

5. The administration of large doses of parathyroid extract, dihydrotachysterol (AT 10), or vitamin D to hypoparathyroid patients all result, like destructive bone disease, in increased urinary excretion of calcium, phosphorus, and magnesium. Balance data reveal that the magnesium losses cannot be accounted for on the basis of changes in the mass or volume of extra-cellular fluid, soft tissues, or of the bone, and indicate a preferential extraction and depletion of magnesium either from soft tissue or bone.

6. Phosphuresis and intra-cellular phosphate depletion are induced by parathyroid extract, dihydrotachysterol and vitamin D. However, intra-cellular phosphate depletion, associated with administration of acetazolamide, does not result in magnesium loss. Available evidence suggests that magnesium is firmly fixed in soft tissues.

7. On theoretical grounds the production and excretion of citrate, which is increased in hypercalciuric states, might account for preferential extraction of magnesium from the bone crystal surface. Preliminary experimental evidence is presented suggesting that this is a reasonable assumption.

8. The concentration of magnesium in serum appears to be governed, in part at least, by the concentrations of calcium and phosphorus.

9. The absorption of magnesium from the intestine may be enhanced by vitamin D, but not in the same degree as calcium.

10. The occurrence of tetany in association with hypocalcemia may be determined in part by the serum magnesium concentration, low levels facilitating, and high levels inhibiting its appearance.

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DISCUSSION

DOCTOR CONRAD: Doctor Eliel, is the formula you presented well enough established so that when you compute the value for phosphorus and calcium, you can rely upon the formula to tell you what the

magnesium concentration should be without actually measuring it?

DOCTOR ELIEL: I don't think the formula is that accurate. Actually, the formula is derived only from the data presented. We haven't tried to apply it to a large enough variety of situations to really establish its validity, but at least it seemed to be an approximate description of the events I presented. I certainly wouldn't want to rely on it for information concerning magnesium levels.

DOCTOR HAMMARSTEN: I would just like to add the comment that really there is no good reason for not measuring the magnesium. It's just as easy to measure as is the determination of calcium, and both can be measured in one determination. This has been the difficulty in this whole field. There have been far too few measurements.

DOCTOR CONRAD: The resemblances between magnesium deficiency states and water intoxication are considerable. Without control studies, and with the doses of magnesium recommended, how can you distinguish between the effect of magnesium itself and any changes in osmolarity it may produce? Will you comment?

DOCTOR ELIEL: As far as our group of patients is concerned, none of them had anything resembling a state of water intoxication. Serum sodiums were normal, for example. We have not done water balances or serum osmolarity determinations which would definitely exclude this possibility.

Clinical Studies in Patients Receiving Long-Term Infusions of Fat Emulsion*

JOHN F. MUELLER
FERNANDO E. VITERI

ALTHOUGH there has been widespread interest in the development of a practical intravenous fat emulsion for human use for many years, the high incidence of untoward reactions to the initial injection has always precluded general acceptance.[1] These acute reactions included: pain, usually in the low-back but often in the chest or extremities; high fever with or without chill; flushing of the skin; nausea and vomiting; dyspnea and cyanosis; rarely, anaphylactoid shock (Table I). However, the accumulated experience of many investigators resulted in an improved fat emulsion which has been available since early in 1956. With its use there has been an almost complete disappearance of untoward reactions with the lone exception of fever.[2] The latter sign occurs in approximately 30% of the patients in whom it is administered, but is mild in nature, delayed, short-lived and in the great majority of patients clinically non-significant. Therefore, from the standpoint of clinical acceptiveness, a usable product is available.

The second problem then had to be faced, i.e., the effect of repeated infusions of fat in the same individual. Until recently there was very little information available concerning this problem in patients receiving the improved emulsion. It would seem that one of the major indications for such a product would be its use in patients requiring long-term therapy. In the Spring of 1957 at the meeting of the Surgeon General's Task Force on Intravenous Fat Emulsions, Upjohn and Levinson[3] and Watkins[4] reported independently on the development and nature of a severe reaction in three volunteers who received multiple infusions of a fat emulsion. This syndrome was characterized by high fever, hepatosplenomegaly, jaundice, anemia, bleeding tendency, abdominal pain, nausea and vomiting. Fortunately all the subjects survived without recognizable sequelae. Although a large battery of laboratory studies were performed, it was not possible in these individuals to establish the exact patho-physiology of the syndrome, but since the recipients of the fat emulsion were ingesting a normal diet it was suggested that this might be an "overloading" syndrome from excess fat. This hypothesis seemed to have some credence since the syndrome had not been observed before in sick patients infused with fat emulsions and receiving most of their caloric demand by vein. Furthermore, there was a suggestion, unproved, that persistent lipemia accompanied the syndrome.

It was clear, therefore, that further observations were necessary in patients receiving multiple infusions of a fat emulsion. An attempt has been made and is still in progress to study systematically various clinical and laboratory parameters in such patients. This report concerns those studies which have been completed. Two patients

*This study was performed under a grant from the Research and Development Division, Office of the Surgeon General, United States Army (Contract No. DA 49-007-MD-800).

CHART DEPICTING REACTION RATES USING THE "OLD" AND "NEW" FAT EMULSION FOR INTRAVENOUS ADMINISTRATION ACCORDING TO NUMBER OF SUBJECTS AND NUMBER OF INFUSIONS

Emulsion	OLD (Aug. '54—Dec. '55)*				NEW (Jan. '56—Oct. '56)			
Number of Infusions:	293				362			
Number of Subjects:	110				151			
Reactions	Number of Infusions	% per Infusion	Number of Subjects	% per Subject	Number of Infusions	% per Infusion	Number of Subjects	% per Subject
Fever**	45	15	32	29	60	17	45	29
Chill	21	7	18	16	2	.6	17	1.3
Back and Chest Pain	38	13	33	30	0	0	0	0
Flushing	7	2	7	6	1	.3	1	.7
Nausea and Vomiting	15	5	14	13	4	1	4	2.6
B.P. Rise and Fall	20	7	14	13	0	0	0	0
Dyspnea Cyanosis	14	5	14	13	0	0	0	0
Shock	2	0.7	2	2	0	0	0	0
Rash	0	0	0	0	1	.3	1	.3
Miscellaneous (Twitching, Itching, Hives, Abd. Cramps)	6	2	6	5	3	.8	3	2
Overall				51%				

*The author is indebted to Doctor Hugo Moeller and Doctor Morton Grossman for some of the data on the "old" emulsion used in this report.

**Over 100.6 orally or 101.6 rectally.

TABLE I

have been investigated intensively and purposefully, while in four others, it has been possible to make only spotty observations.

Methods

M.J. was a 45 year old white woman admitted to the Medical Service of the Cincinnati General Hospital because of malnutrition. Complete physical and laboratory examination failed to reveal any pathologic cause. She weighed 77 pounds at the time of admission. Six hundred cc. of Lipomul,* intravenous, was administered daily for 17 days.

E.B. was a 44 year old white woman admitted to the Psychosomatic Ward of the Cincinnati General Hospital because of a long history of functional gastrointestinal symptoms, severe psychoneurosis, hysterial syncope, weight loss and diarrhea. She weighed 83 pounds at the time of admission. After intensive diagnostic work-up failed to reveal any significant organic pathology, she was given 600 cc. of Lipomul* intraenously each day for 24 days.

Both subjects were given the Lipomul early in the morning according to the technique previously described.[2] They were examined each day by a physician for any change in the physical status. Laboratory procedures were carried out at appropriate intervals.

The routine laboratory tests were performed according to standard techniques. The TAMe assays for prothrombin were carried out in Doctor Helen Glueck's laboratory according to the procedure previously published.[5] The optical density of the serum was measured in a Coleman Jr. spectrophotometer at 700 *mu* using water as the blank. Cr^{51} and Fe^{59} were used to study life span and iron turnover and red cell uptake respectively according to established methods, with the help of Doctor Ben Friedman of the Radio-isotope Laboratory. In this laboratory, the apparent red cell half-life is normally 30 days. Plasma iron turnover is 0.4 - 0.8 mg/day/100 ml blood. Red cell uptake is normally over 75% after 14 days.

Results

1. Clinical: In both patients the infusions were discontinued at 24 and 17 days respectively because of the occurrence of a clinical picture which was similar in nature and vomiting (Figures 1 and 2). In both instances there was some decrease in oral caloric intake prior to the onset of the re-

*Lipomul, Upjohn, is a 15% cottonseed oil emulsion, emulsified with 1.2 Gm.% soybean phosphatide, .3% Pluronic F68, 4% Dextrose and was kindly furnished by Doctor E. A. Hawk, The Upjohn Company, Kalamazoo, Michigan.

but more severe in E.B. than M.J. This syndrome was manifested by fever, hepatomegaly, abdominal pain, anorexia, nausea

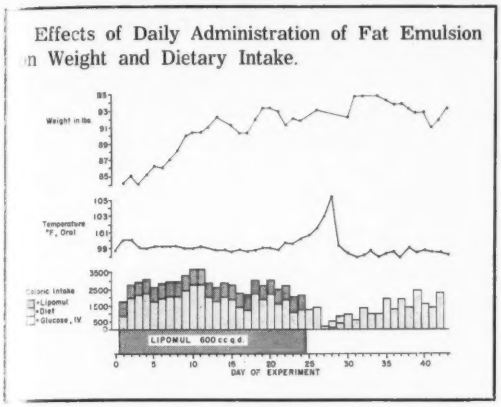

Figure 1.

action. In E.B. intravenous hydrocortisone produced an immediate lysis of the fever and an uneventful recovery ensued. Hepatomegaly subsided over the period of several days. In the case of M.J. simple discontinuation of the fat emulsion resulted in a gradual return of her pre-infusion state of health. In neither instance were any demonstrable residuals noted.

It should be noted that a significant weight gain occurred in each patient. There was an associated increase in appetite early in the infusion period as evidenced in Figures 1 and 2. Both patients related subjecrise in reticulocytes. At the height of the anemia, fecal urobilinogen was normal and occult blood was not found in the stool. No appreciable change in the white cells or

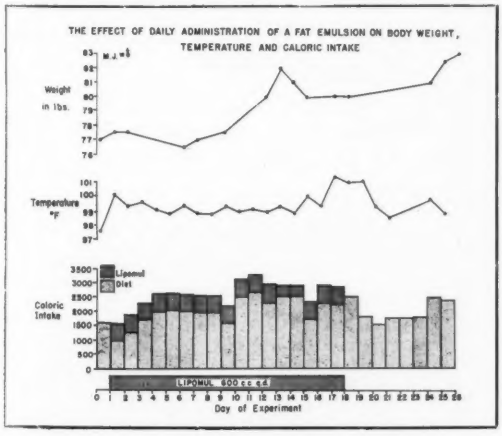

Figure 2.

tive increase in sense of well-being during the early infusion period.

2. Hemogram: In E.B. there was a slow decline in hematocrit, red cell count and hemoglobin after the second week (Figure 3). This was associated with a slight

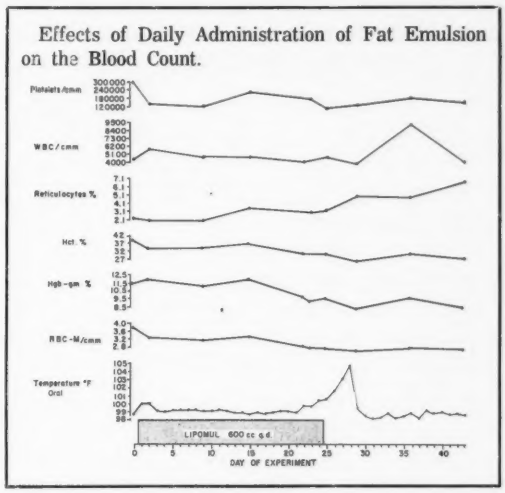

Figure 3.

platelets was found. The isotope studies were performed on the first day and repeated on the day following the acute febrile illness. The apparent red cell half-life was 17.7 days on the first study and 14.3 days on the second. Plasma iron turnover was 0.6 mg/day/100 ml of blood initially and 0.44 mg/day/100 ml at the end. The red cell uptake of radio-iron after 14 days was normal in both instances. The serum iron levels were low normal and likewise did not change. It should be mentioned that a total of 545 cc. of blood were withdrawn from this patient over the period of the study.

The hemoglobin in M.J. showed a slight fall after the first week, but no progressive change throughout the remainder of the experiment (Figure 4). An anemia developing in the post-infusion period has not been explained. No significant change was apparent in the white cells or platelets. No isotope studies were performed in this subject.

Bone marrow aspiration in E.B. before and after the experimental period showed slightly more fat in the post-infusion specimen but otherwise no significant change was evident.

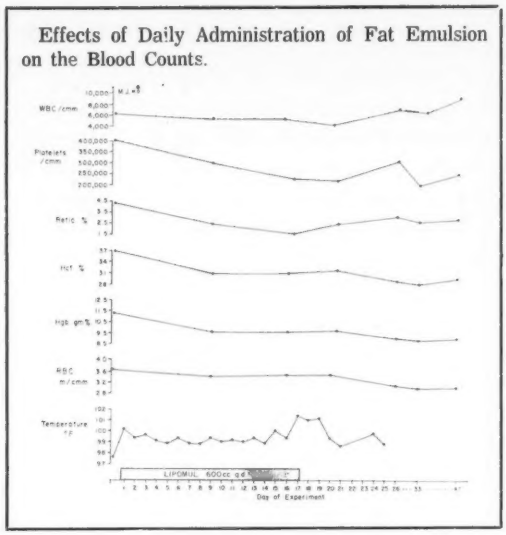

Figure 4.

3. Liver Studies: Complete function studies were performed on E.B. The only abnormality was a progressive rise in BSP retention (Figure 5). This peaked at 23.5% the day following the lysis of fever and then promptly returned to normal. In M.J. only the BSP and bilirubin were measured. The former showed a rise from 1.5% to 10%, but no change in bilirubin occurred.

In M.J. a liver biopsy was obtained before and 5 days after the infusion period. At the time of the second biopsy, the liver

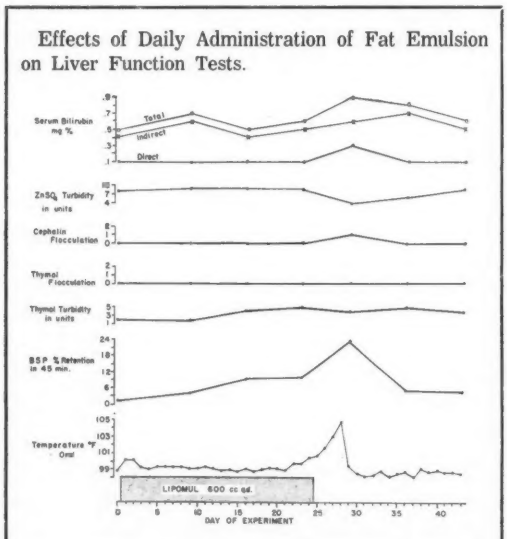

Figure 5.

was still grossly enlarged, although somewhat smaller than at the height of the reaction. The initial biopsy was reported as showing no diagnostic abnormalities. The second biopsy revealed scattered microgranulomas of non-specific nature. There was no evidence of pigment or abnormal lipid deposition. Repeat biopsy 10 weeks after the second showed one area of non-specific focal necrosis and an otherwise normal histologic picture.

4. Lipid Studies: The serum remained clear twenty-four hours after each infusion in both cases as measured by optical density. Clearing studies likewise did not show any tendency toward slower clearing with successive infusions. However, there was a slight rise in total fatty acids, presumably soluble lipoprotein, which in E.B. was almost exclusively due to a large increment

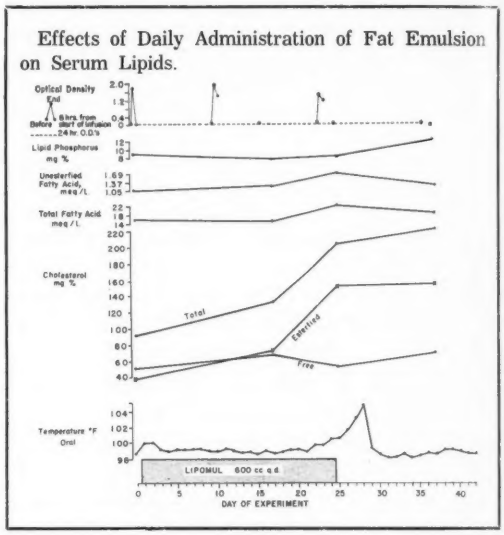

Figure 6.

in serum esterfied cholesterol (Figure 6). Only a slight rise in the serum cholesterol occurred in M.J. (Figure 7).

5. Coagulation Studies: In both patients, studies were calculated to assay not only the long-term effect of multiple infusions of fat, but also the immediate effects of fat infusion on the coagulation mechanism. The latter would appear to reflect hypercoagualability at the height of lipemia as evidenced by decreased silicon clotting times and increased prothrombin conversion.

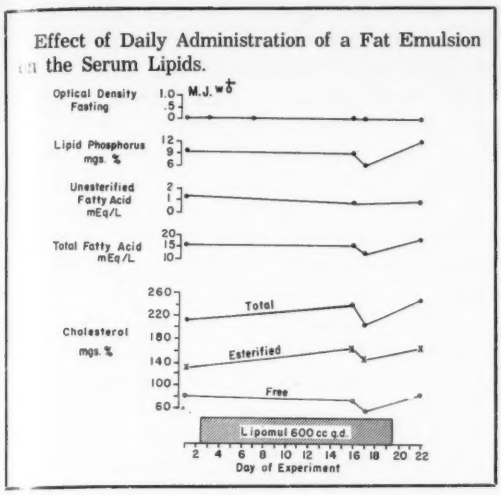

Figure 7.

However, progressive fall in the plasma prothrombin and slight falls in the accessory factors after many infusions reflect hypocoagulability (Tables II and III). The oral administration of 10 mg. of Vitamin K_1 oxide daily to M.J. had little effect upon the slightly lowered prothrombin time, raising it from 40.2 TAMe units to 44.1 units in 72 hours.

Discussion

There seems to be slight doubt that both of the subjects experienced a reaction to the long-term administration of an intravenous fat emulsion. The mildness of the reaction in M.J. may reflect the fact that she received less in total amount, or more likely that there are and will be individual variations in susceptibility to the reaction. The syndrome was strikingly similar to those previously reported.[3,4] However, until more cases have been studied, its expected incidence is impossible to predict. The studies performed in these two patients may give some hints as to possible etiologic factors.

Both of the reported patients were consuming an adequate diet during the infusion period. This was also true of the previously described cases. This suggests that the excess fat in the emulsion, which presumably is not required, may be inefficiently handled, back-up in the tissue and finally in the blood and thereby produce the "overloading" syndrome. The lipid studies in this report do not support the existence of lipemia but do not eliminate the possibility of tissue deposition. The liver biopsy on M.J. at the time of reaction, however, did not show any fatty infiltration but rather some non-specific micro-granulomas. The interpretation of the significance of the latter is open to question.

The cause of the anemia in E.B. is not explained. Unfortunately the initial red cell half-life was abnormal so that the slight shortening from 17.7 to 14.3 days is difficult to interpret. However, the normal serum bilirubin and fecal urobilinogen would seem to rule out a hemolytic process. The

EFFECTS OF INTRAVENOUS FAT ON COAGULATION MECHANISMS

Date	7-31-57	8-6-57		8-12-57		8-20-57		8-23-57		9-3-57	9-6-57	9-17-57
		Before	After	Before	After	Before	After	Before	After			
Siliconized Lee White Clotting Time												
1st Tube	4 min.	14 min.	6 min.	9 min.	——	——	6 min.	9 min.	6 min.	22 min.	8 min.	6 min.
2nd Tube	——	19 min.	8 min.	14 min.	——	——	12 min.	14 min.	——	41 min.	12 min.	12 min.
3rd Tube	26 min.	25 min.	——	20 min.	——	——	12 min.	18 min.	——	60 min.	16 min.	17 min.
Plasma Prothrombin Time												
Control	11.4 sec.	——	13 sec.	13.0 sec.	——	——	13.0 sec.	12.7 sec.	——	11.6 sec.	11.1 sec.	10.5 sec.
Patient	11.9 sec. (95%	——	11.5 sec. (100%	11.5 sec. (100%	——	——	12.5 sec. (100%	11.2 sec. (100%	12.6 sec. (100%	16.0 sec. (57%	13.7 sec. (70%	11.2 sec. (97%
Serum Prothrombin Time												
28° Serum												
20 min. inc.	11.3 sec.	——	<60 sec.	8.8 sec.	——	——	8.5 sec.	8.7 sec.	10.9 sec.	10.5 sec.	10.2 sec.	9.5 sec.
40 min. inc.	132 sec.	——	<60 sec.	9.9 sec.	——	——	9.5 sec.	11.0 sec.	10.9 sec.	11.9 sec.	12.1 sec.	9.8 sec.
60 min. inc.	602 sec.	——	<60 sec.	22.4 sec.	——	——	17 sec.	13.6 sec.	48.8 sec.	11.6 sec.	13.4 sec.	15.2 sec.
Plasma Tame Assays	35 u/ml	——	38 u/ml	32 u/ml	——	——	28 u/ml	32 u/ml	39 u/ml	10 u/ml	28 u/ml	49 u/ml
Serum Tame Assays												
20 min.	27 u/ml	——	1 u/ml	20 u/ml	——	——	5.0 u/ml	34 u/ml	7 u/ml	4 u/ml	0	36 u/ml
40 min.	12 u/ml	——	1 u/ml	11 u/ml	——	——	5.0 u/ml	5 u/ml	7 u/ml	0	0	13 u/ml
60 min.	8 u/ml	——	2 u/ml	6 u/ml	——	——	8.2 u/ml	6 u/ml	6 u/ml	0	0	7 u/ml
Factor V	normal		normal	normal			normal	normal	normal	slight fall	normal	normal
Factor VII	normal		normal	normal			normal	normal	normal	normal	normal	normal

TABLE II.

moderate depression of plasma radio-iron turnover suggests decreased erythropoiesis, but normal red cell radio-iron uptake and mild reticulocytosis make this possibility less likely. Further studies are certainly indicated and are in progress. It would seem, however, that anemia is not a prominent etiologic factor in the febrile syndrome.

Hepatic necrosis or failure is not suggested by the findings. The elevation of the BSP has been a common observation by most investigators. It is thought that this reflects merely a temporary "clogging" of the Kupffer cells of the liver by fat or its products and thus reduces their efficiency in clearing the blood of the injected dye. Certainly the abnormality rapidly disappears following cessation of the infusions. No other abnormalities are apparent in the liver profile which support previous data on the effect of I. V. fat emulsions in patients with liver disease.[6] The non-specific microscopic abnormalities in the liver reported in M.J. are not entirely explicable but would not appear to be extensive enough to be considered causal of the reaction. Unpublished observations by our group have failed to reveal any abnormality of the fasting serum proteins by electrophoresis in patients receiving multiple infusions of Liposyn.

The coagulation studies are considered important although their relationship to the chronic reaction is not clear. Phospholipids have known thromboplastic activity. Their presence in the emulsion as emulsifiers may well be responsible for the hypercoagulability noted immediately following each infusion. These observations have been extended in Doctor Glueck's laboratory and show that in most patients there is a shortening of silicon clotting times and increased prothrombin conversion at the end of the fat infusion. The particulars of these studies will be the subject of another report. The hypocoagulability noted at the end of the infusion period in E.B., and suggested by the bleeding tendency in previously re-

THE EFFECT OF INTRAVENOUS INFUSION OF A FAT EMULSION ON BLOOD COAGULATION

	10-15-57		10-16-57		10-17-57		10-22-57		10-29-57		11-5-57	
M.J. wŏ	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Siliconized Lee-White Clotting Time (min.)												
1st. Tube	12		12		16	4	12	5				
2nd. Tube	19		22		24	8	14	7				
3rd. Tube	23		30		25	16	17	8				
Plasma Prothrombin Time (min.)												
Control							12.4		11.2		10.6	
Patient	14				10.4	11.4	11.3	12.7	11.3		10.3	
Serum Prothrombin Time (min.)												
20 min.	12.3		8.9		10.3	9.7	9.8	10.5				
40 "	14.5		10.2		37.5	14.2	21.6	22.7				
60 "	19.2		11.2		29.2	22.5	43.5	>60				
Plasma Tame Assay (units)	55.5		61.6				36.6	32.4	40.2		41.0	
Serum Tame Assay (units)												
20 min.	9.3		24.5		1.2	3.7	25.9	2.8				
40 "	5.4		14.3		1.9	7.3	1.7	0				
60 "	0		11.6		1.7	3.6	3.1	3.0				

TABLE III.

ported cases, might be explained by repeated episodes of hypercoagulability at the height of lipemia following each fat infusion with eventual depletion of certain clotting factors. This is strictly conjectural and will require much more proof before being accepted as fact. However, the effect of fat on coagulation mechanism is of vast importance not only as concerns the problem of intravenous feeding, but its role in the causation of coronary thrombosis. Further careful work is needed in this field.

The prompt, almost dramatic, response of the febrile reaction to the intravenous hydrocortisone in E.B. may be a hint as to the nature of the reaction. The clinical observation was striking. It suggested that hypersensitivity might be invoked. The microgranulomas of the liver would be consistent with such a concept. It would be difficult to prove or disprove such a hypothesis with the data now available.

Therefore, one must conclude that at the moment there is no good explanation for the febrile reaction to multiple infusions of fat emulsions. It may be a consequence inherent in the administration of so much lipid to an individual in positive caloric balance. This is suggested by the fact that multiple infusions to sick patients, all of whom were calorically deficient, both by the author and others, has not resulted in such a severe clinical state as described above. (The similarity of the clinical state to that of idiopathic hyperlipemia is striking and allows for much idle speculation in that direction.) However, only much more experience will answer this important question. At the moment it would seem that prolonged administration of a fat emulsion to any patient should be accomplished with care and the realization that such a reaction as herein described might occur.

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Physiological Observations on Fat Transport Utilizing an Intravenous Emulsion*

JOHN F. MUELLER
JACK IACONO

IN A PREVIOUS PUBLICATION, the relationship between the acute febrile reaction to a single infusion of a fat emulsion and the rapidity of its removal from the blood stream was discussed.[1] That study grew out of the observation that purification of the soybean phosphatide emulsifier reduced drastically the incidence of acute reactions to a fat emulsion with one prominent exception—fever. The latter occurred in exactly the same percentage of patients when the improved emulsion was given as it did when the highly reactive emulsion was administered. More recent confirmatory data accumulated in 31 patients receiving 127 infusions at the Cincinnati General Hospital shows that 26% of the subjects had a delayed type febrile reaction. Thus it has been suggested that the febrile reaction is perhaps "physiologic" in nature. This is supported by the fact that rapid disappearance of the infused fat from the blood is associated with a high incidence of febrile reactions whereas delayed clearance is accompanied by a very low incidence of fever (Figure 1). It has been ventured that endogenous heat produced by rapid oxidation of the rapidly cleared fat in a susceptible individual might be responsible for the fever. However, there was no proof that rapidly cleared fat was necessarily rapidly oxidized. Therefore, an attempt to correlate ketone production with fat clearance was made and is the basis of part of this report.

The marked variation of clearing patterns with the same individual under variable circumstances as well as between different individuals was pointed out (Figure 2). This suggests that there is a highly significant physiologic mechanism for clearing infused fat from the blood and that this mechanism is probably effected by various stimuli.

*This study was performed under a grant from the Research and Development Division, Office of the Surgeon General, United States Army (Contract No. DA 49-007-MD-800).

Relation Between The Optical Density of the Plasma 8 Hours After The Start of an Infusion of 600 ml of Lipomul and the Highest Rectal Temperature in the 12 Hour Post-Infusion Period in 95 Subjects Receiving Their First Infusion.

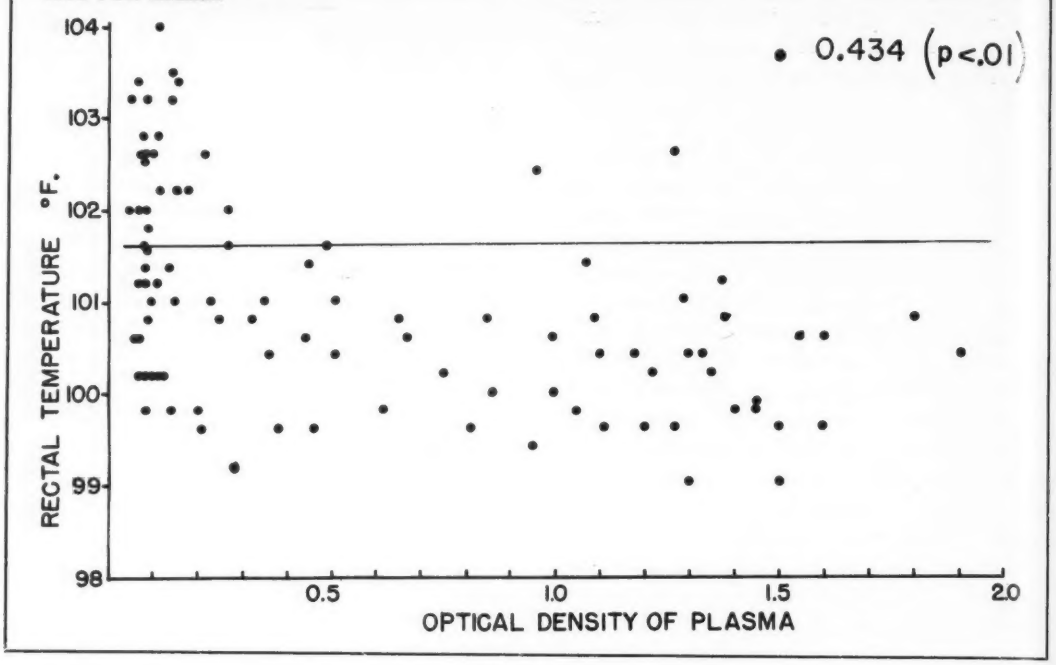

Figure 1.

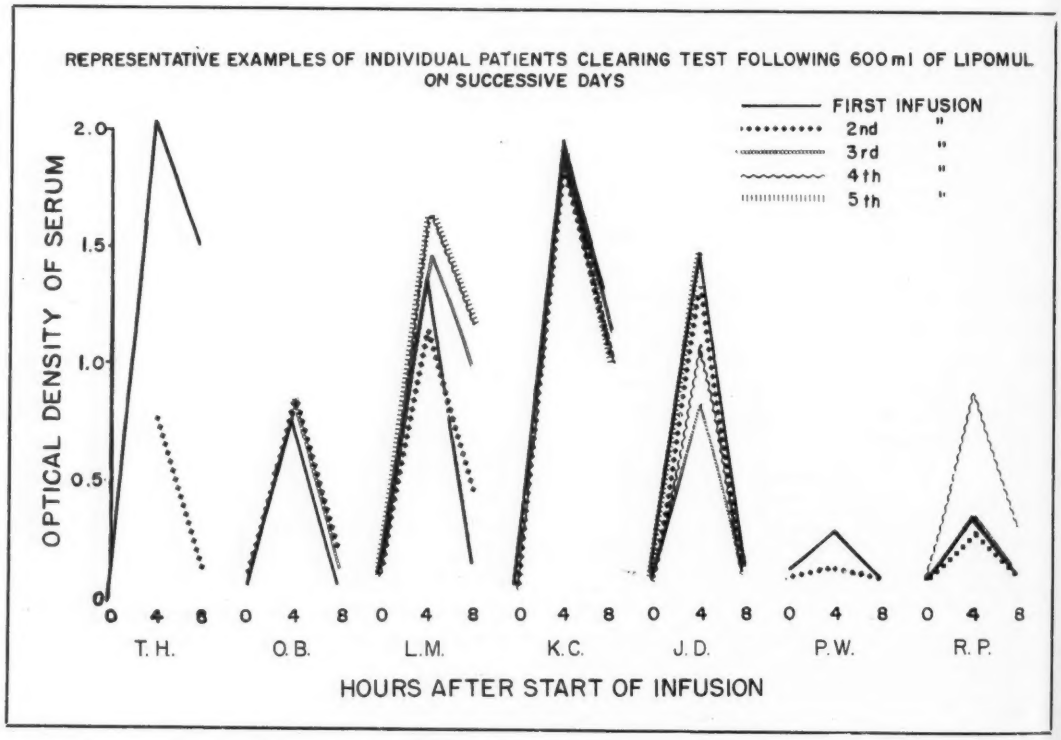

Figure 2.

In an effort to better understand the physiologic process behind clearing of the blood, "clearing factor enzyme" or lipoprotein lipase was studied in our patients. This is the substance first described by Hahn which can be demonstrated in the blood of animals and man following the administration of heparin or heparin-like substances, and which produces clearing by hydrolysis of the fatty acid moiety. Iacono and Cleland from our laboratory showed that without heparin, the concentration of this enzyme was so low as to account for only 5% of the clearing of the infused fat emulsion.[2] Thus if lipoprotein lipase is physiologically significant in the actual clearing of the blood, it must function at the cell level rather than intravascularly.

In an attempt to gain some insight into the perplexing problems, various clinical parameters and disease entities were correlated with clearing patterns without avail (Table I). At this point it was decided to look at the role of the various serum lipids during clearing. The first study was performed in nine hospitalized patients and nine healthy volunteers. These preliminary results led us to intensively study the changes in serum lipid patterns under varying conditions following intravenous fat in 10 healthy volunteers. These findings corraborated the preliminary ones and are the basis of the latter half of this report.

Methods

For the ketone study, 11 patients from the wards of the Cincinnati General Hospital were randomly chosen and infused with 600 cc. of Lipomul. The patients were fasting during the entire procedure. The Lipomul was administered at a constant rate of 64 ggts/min., requiring approximately 3½ hours total time. Blood was drawn before, at the end, and 8 hours after the beginning of each infusion and analyzed for total ke-

THE RELATION OF VARIOUS PHYSIOLOGIC PARAMETERS AND DISEASED STATES AND THE PATTERN OF CLEARING OF THE BLOOD FOLLOWING AN INFUSION OF A FAT EMULSION

		Clearing Pattern				
	Total	Intermediate*		Slow**	Fast***	
Weight	No.	No.	(%)	No. (%)	No.	(%)
Less than 100 lbs.	8	6	(75)	2 (25)	0	(0)
100 - 150 lbs.	76	27	(35)	28 (36)	21	(29)
150 - 200 lbs.	14	6	(43)	6 (43)	2	(14)
Over 200 lbs.	1	0	(0)	1 (100)	0	(0)
Blood Pressure						
Diastolic above 90 mm Hg.	28	16	(57)	8 (28)	4	(15)
Diastolic below 90 mm Hg.	77	28	(36)	29 (37)	20	(27)
Age						
20 - 40 years	21	7	(33)	12 (57)	2	(11)
40 - 60 years	39	11	(28)	20 (51)	8	(21)
60 - 80 years	54	28	(52)	11 (20)	15	(28)
Clinical Diagnosis						
Hyperlipemia	1	0	(0)	1 (100)	0	(0)
Diabetes Mellitus	2	1	(50)	1 (50)	0	(0)
Coronary occlusion	5	1	(20)	4 (80)	0	(0)
Stroke	7	3	(43)	4 (57)	0	(0)
Arteriosclerotic heart disease	9	4	(44)	1 (12)	4	(44)
Generalized Arteriosclerosis	17	8	(47)	4 (23)	5	(30)
Family history of any of the above	21	6	(28)	11 (52)	4	(20)
Cirrhosis of liver	11	0	(0)	10 (91)	1	(9)
Normal volunteers	18	6	(33)	12 (66)	0	(0)

*Intermediate—O. D. above 1.0 at end of infusion, below 0.3 after 8 hrs.
**Slow—O. D. above 1.0 at end of infusion, above 0.3 after 8 hrs.
***Fast—O. D. below 1.0 at end of infusion, below 0.3 after 8 hrs.

TABLE I

tone bodies by a modification of the orginal method of Greenberg and Lester.*[3] These times were chosen not only to conform to previous clearing studies, but because preliminary work showed that they represented the peak and return toward normal in most patients. At the same time that blood ketones were done, the optical density of the serum was also measured by previously described methods, to assess the rapidity of clearing.

For the serum lipid study, 10 conscientious objectors on the metabolic ward at the United States Army Medical Nutrition Laboratory, Fitzsimons Army Hospital, Denver, Colorado were divided into two groups of six and four each. The group of six was subdivided into two groups of three, one group receiving 600 cc. of Lipomul intravenously and the other 600 cc. of Lipomul intragastrically. One week later the procedure was reversed. Blood was withdrawn from each subject before, at the end, 8, 16, 24, 36, and 48 hours after the beginning of each experiment. The second group of four subjects each received 600 cc. of Lipomul intravenously each day for five consecutive days. On the first, third and fifth days, blood was withdrawn from each subject before, at the end, 8, 16, and 24 hours after the beginning of the daily infusion. On the final day 36 and 48 hour bloods were also drawn.

The blood was chilled immediately upon withdrawal, the serum separated at ordinary centrifugal force and aliquot specimens taken for analyses. The remainder of the serum was then spun at top speed in a highspeed Servall supercentrifuge for 45 minutes (approximately 18,000 rpm). The subnatant serum was then removed and analyzed. The whole serum and subnatant were analyzed for total fatty acid by the method of Smith and Kik,[4] total and free cholesterol by a modification of the Sperry-Schoenheimer method,[5] lipid phosphorous by the method of Fiske and Subbarow,[6] and neutral fat by difference (TFA - [CE + PL] = NFA).

The possible effect of diet was appreciated so that the subjects in the second group receiving the multiple infusions were fed a constant, known diet in which the Lipomul was substituted isocalorically for fat during the infusion period. All infusions were started in an overnight-fasting state.

Results

The values for blood ketones rose in each subject immediately after the infusion and returned toward normal after 4½ more hours in all except one patient (Figure 3).

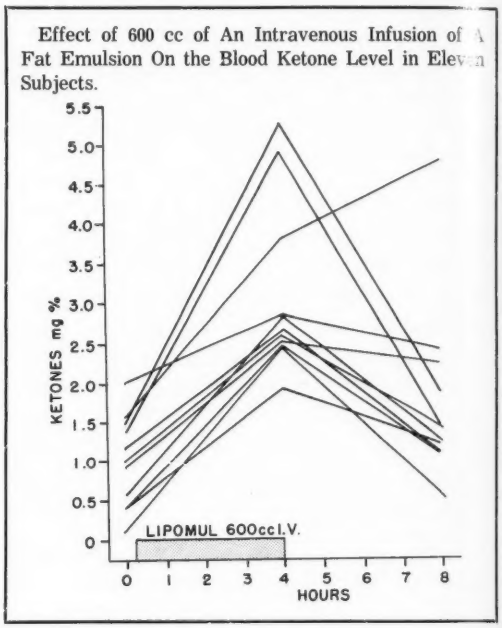

Figure 3.

However, it was surprising that the rise was so small considering the amount of fat, namely 90 Gms, infused so rapidly. These rises really are quite small, perhaps insignificant, but consistent. At attempt to correlate the optical density at the end of the infusion and the blood ketone at the same time results in an inconclusive graph (Figure 4). It should be noted that the patient with the highest ketone level was a very rapid clearer; however, the most rapid clearer was the poorest ketone producer. This dichotomy is explainable by the fact that it occurred in a severely ill patient with cirrhosis of the liver and impending hepatic coma in whom ketone production is notoriously inefficient. This type of experiment was abandoned because it was felt the small rises

*The author wishes to thank Doctor E. Werk, Chief Metabolic Division, Cincinnati Veterans Administration Hospital for performing the analyses for blood ketones.

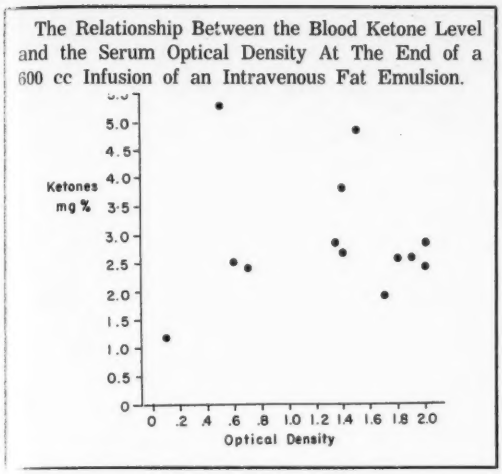

Figure 4.

ketones following I.V. fat could not be used to access oxidation. Presumably under the conditions of the experiment, the oxidized 2-carbon fragments enter the citric acid cycle immediately so that acetone bodies do not have a chance to form. Therefore, other means must be sought to prove that rapid clearing of the blood necessarily means rapid oxidation of the infused fat.

The changes in serum lipids can best be described by referring to Figures 5 through 12. The subnatant values are interpreted as representing the lipid associated with solubilized fat or lipoprotein wheras the difference between whole serum and subnatant would represent the lipid mainly in the insoluble chylomicron and perhaps some very low density lipoprotein. There is a great quantitative difference between the effect on serum lipids of oral and I.V. Lipomul but very little qualitative differences. All changes are in the same direction. The single-infusion induced alterations in the six subjects in one group are similar to those in the four subjects after their first infusion.

The total fatty acids reach their peak in the whole serum immediately after the completion of the infusion and then rapidly return toward normal (Figures 5 and 6). The much lower peak in subnatant total fatty acids is reached four hours after that in whole serum and tends to be biphasic, rising again at 36 and 48 hours. The delayed rises in total fatty acids are interpreted as representing solubilized or lipoprotein increases consequent to the infused fat leaving the blood and then re-entering the circulation to be carried to the cell for either storage or energy. With repeated infusions there is a progressive rise indicating some tendency for slower clearing of the blood with successive infusions. Neutral fat patterns follow the total fatty acid picture quite closely (Figures 7 and 8).

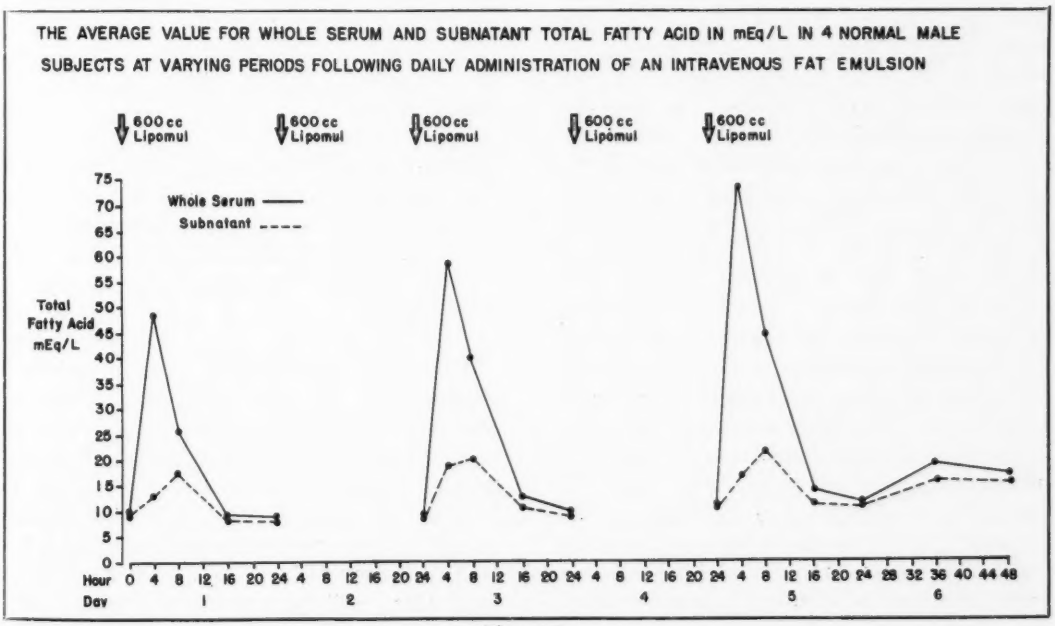
THE AVERAGE VALUE FOR WHOLE SERUM AND SUBNATANT TOTAL FATTY ACID IN mEq/L IN 4 NORMAL MALE SUBJECTS AT VARYING PERIODS FOLLOWING DAILY ADMINISTRATION OF AN INTRAVENOUS FAT EMULSION
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
Whole Serum
Subnatant
Total Fatty Acid mEq/L
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Hour 0 4 8 12 16 20 24 4 8 12 16 20 24 4 8 12 16 20 24 4 8 12 16 20 24 4 8 12 16 20 24 28 32 36 40 44 48
Day 1 2 3 4 5 6

Figure 5.

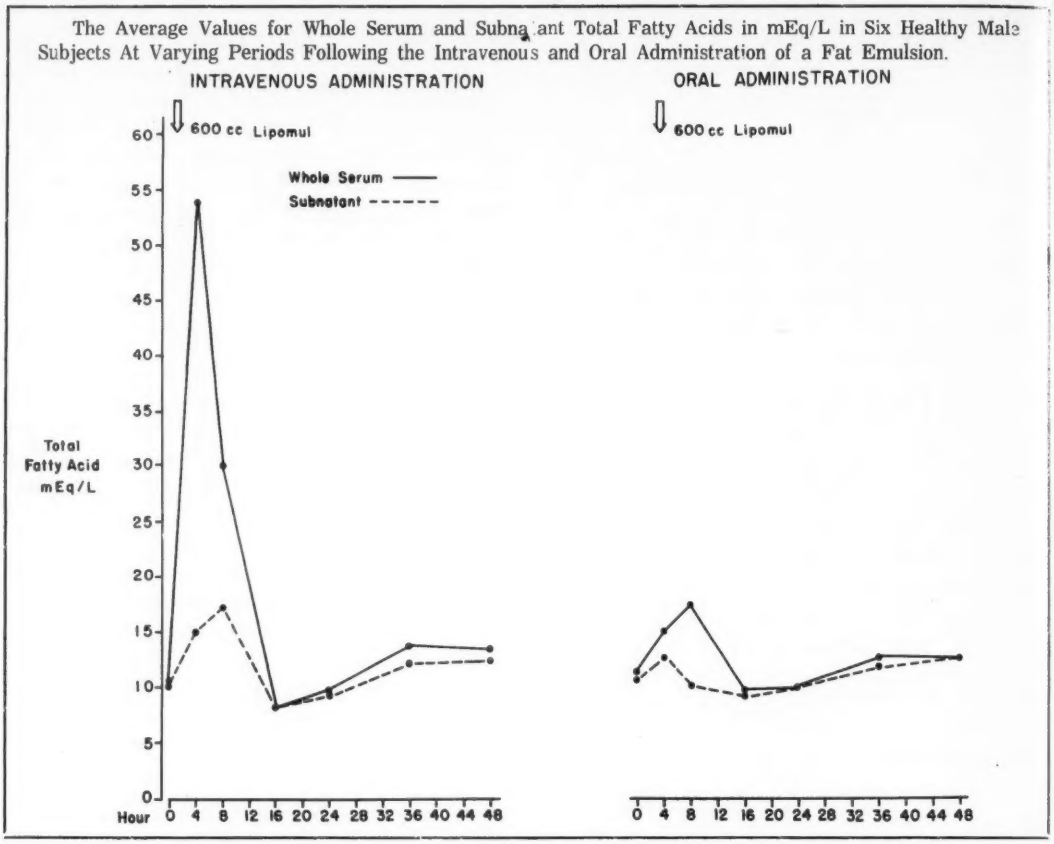

Figure 6.

The changes in the serum cholesterol were striking (Figures 9 and 10). With the initial infusion there is a slight rise in the whole serum total cholesterol reaching its peak either at 4 or 8 hours. The rise can not be accounted for by the Lieberman-Baurshard reacting material infused in the Lipomul. This must represent endogenous free cholesterol. Following the rise there is an abrupt fall, the lowest point occurring at 24 hours. The changes are entirely different in the subnatant, where the total cholesterol falls abruptly from the beginning. This difference between whole serum and subnatant suggests that serum cholesterol is moving into the chylomicron layer initially and then disappearing from the blood in this fashion. Similar but less dramatic changes occur following oral Lipomul. With successive infusions the above changes are intensified early, but by the fifth infusion very little total diminution occurs. Following discontinuation of the infusions there is an immediate rise toward pre-infusion levels. It will be seen from the graphs that all of the late fall in cholesterol is in the esterified fraction, while the early rise is in the free fraction.

The changes in lipid phosphorous were not especially unusual (Figures 11 and 12). The immediate rise was easily accounted for by the soybean phosphatide employed as the emulsifier in the emulsion. The fall seemed to follow the changes in total fatty acid.

Discussion

The above findings are preliminary and abbreviated. A more complete report is forthcoming. From previous observations concerning the clearing pattern of intravenous emulsions in various individuals, it is clear that what is found in these normal, healthy, young men may not necessarily be true in women or in older, ill patients. However, since so little is really understood concerning the pathways whereby fat is moved

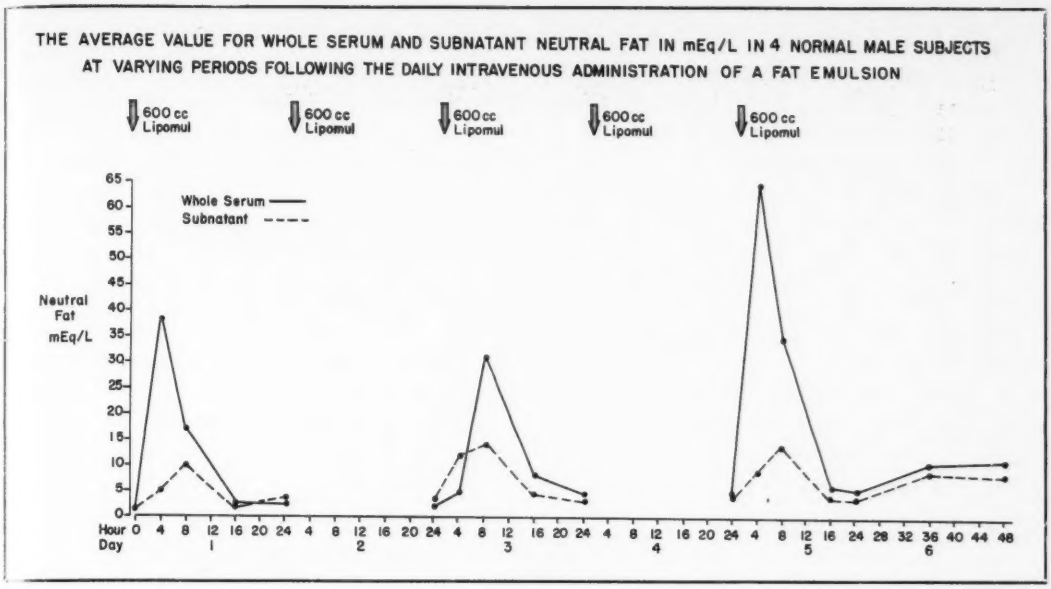
THE AVERAGE VALUE FOR WHOLE SERUM AND SUBNATANT NEUTRAL FAT IN mEq/L IN 4 NORMAL MALE SUBJECTS AT VARYING PERIODS FOLLOWING THE DAILY INTRAVENOUS ADMINISTRATION OF A FAT EMULSION
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
Whole Serum
Subnatant
Neutral Fat mEq/L
Hour
Day

Figure 7.

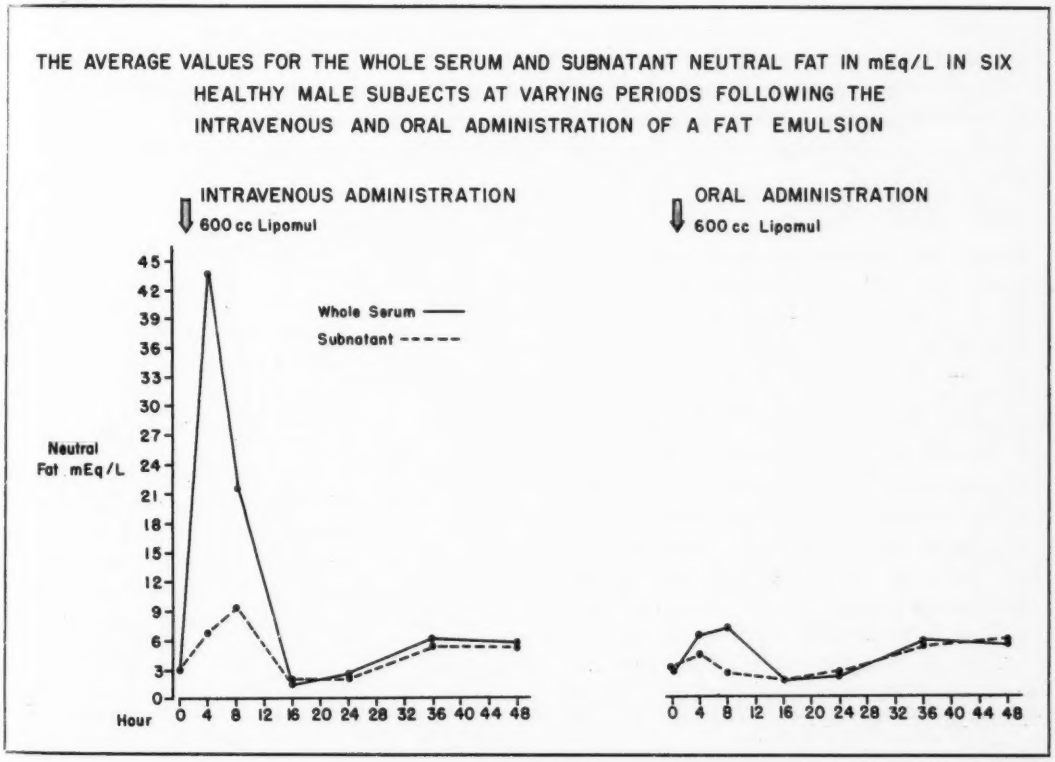
THE AVERAGE VALUES FOR THE WHOLE SERUM AND SUBNATANT NEUTRAL FAT IN mEq/L IN SIX HEALTHY MALE SUBJECTS AT VARYING PERIODS FOLLOWING THE INTRAVENOUS AND ORAL ADMINISTRATION OF A FAT EMULSION
INTRAVENOUS ADMINISTRATION
600 cc Lipomul
ORAL ADMINISTRATION
600 cc Lipomul
Whole Serum
Subnatant
Neutral Fat mEq/L
Hour

Figure 8.

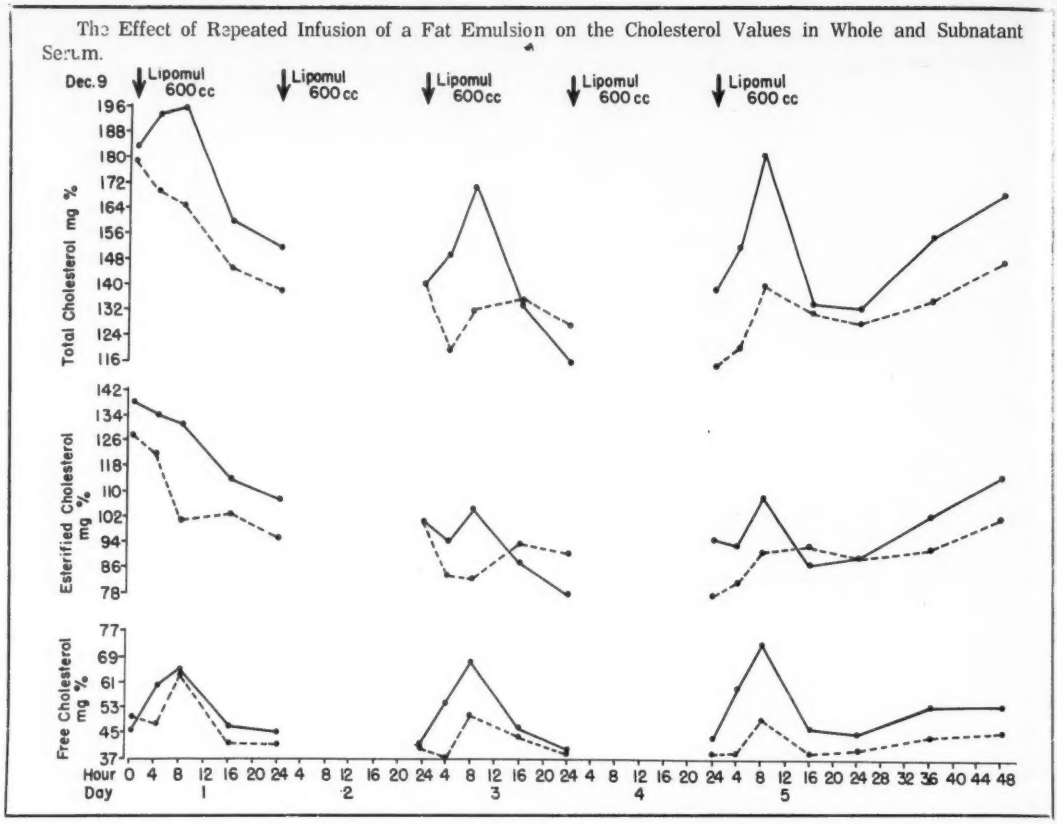

Figure 9.

from the blood to the liver and thence to the cell for energy or storage, certain hypotheses can be postulated from our observations. They are by no means proved.

The extent of intravascular vesus intracellular lipolysis has been argued for many years. The previously mentioned studies of Cleland and Iacono in which a very insignificant amount of "clearing factor enzyme" was found in the blood of our patients suggested that very little hydrolysis of the fatty acid chain occurred intravascularly. The very slight and delayed rise in subnatant total fatty acids following intravenous fat as compared to the rise in whole serum suggests that very little triglyceride fat is undergoing lipolysis in the blood but rather that it is being removed from the blood in the form of chylomicrons, hydrolyzed and then re-entering the blood in the form of lipoprotein to be transported to the cell. The most likely site for this to occur is in the liver. The secondary rise in total fatty acids that occurs in 36 or 48 hours probably represents a delayed increased production of lipoprotein consequent to the large fat load.

The daily increases in the height of the total fatty acids, following the infusion is explained by gradual overloading of the physiological clearing mechanism, whatever that may be. This phenomena of decreased tolerance to a fat load appears to be quite variable among individuals and may reflect the subject's need for energy. Thus, in our experience, patients who have a caloric need for the fat will clear their blood more rapidly and therefore have a greater tolerance in terms of accumulating fat in their blood at any given time than healthy individuals. Presumably prolonged hyperlipemia following fat infusions would be inadvisable, so that frequent observations of a patient's serum for lipemia is strongly urged in all subjects receiving multiple infusions.

The role of serum cholesterol in lipid

transport and metabolism has been a controversial subject. The immediate rise in whole serum free cholesterol suggests that the fat load called forth either stored or newly synthesized endogenous cholesterol. This cholesterol plus some of that already present in soluble lipoprotein moved readily into the unsoluble or chylomicron layer. The latter undoubtedly contains or is, in fact, very low density lipoprotein. This observation suggests that the high density lipoprotein can become low density lipoprotein perhaps within the blood stream merely by the addition of lipid molecules to its structure. Regardless of where this transportation is accomplished, cholesterol in the esterified form then leaves the blood stream with the chylomicron. The ultimate fate of a particular cholesterol molecule is not shown by these studies, but presumably the serum depression is very transitory since it starts rising 24 hours after the last infusion. It is interesting to speculate concerning the cholesterol-lowering potentials of such an emulsions since it contains a highly unsaturated oil, cottonseed oil. There is an increasing amount of data in the literature concerning the cholesterol-lowering potentiality of dietary unsaturated fat in humans.[7] It would be dangerous to relate acute changes such as we are reporting to prolonged effects. The acute effects can be reproduced by the emulsifier or glucose alone, and therefore are not specific for the fat. Furthermore, in our experience there has been no consistent variation in total

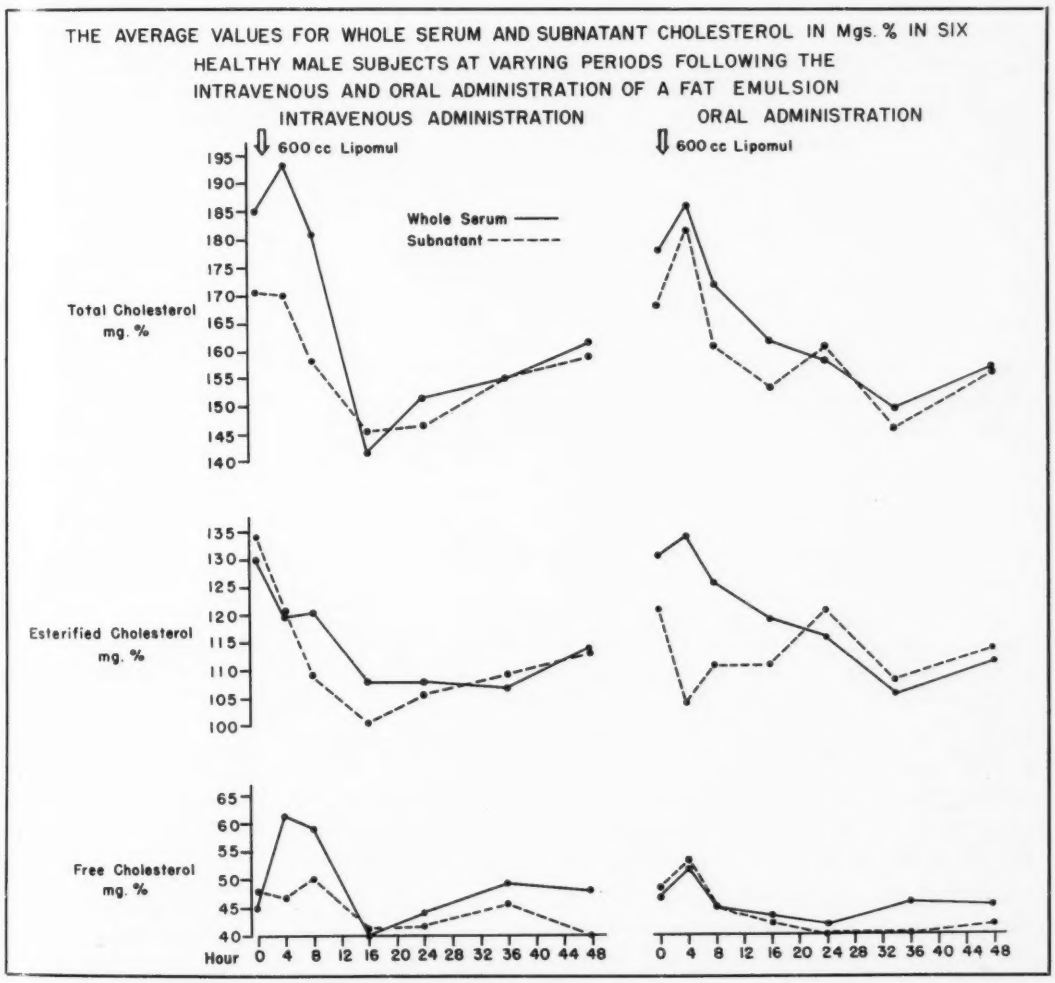
THE AVERAGE VALUES FOR WHOLE SERUM AND SUBNATANT CHOLESTEROL IN Mgs. % IN SIX HEALTHY MALE SUBJECTS AT VARYING PERIODS FOLLOWING THE INTRAVENOUS AND ORAL ADMINISTRATION OF A FAT EMULSION
INTRAVENOUS ADMINISTRATION
ORAL ADMINISTRATION
600 cc Lipomul
600 cc Lipomul
Whole Serum
Subnatant
Total Cholesterol mg. %
Esterified Cholesterol mg. %
Free Cholesterol mg. %
Hour
0 4 8 12 16 20 24 28 32 36 40 44 48

Figure 10.

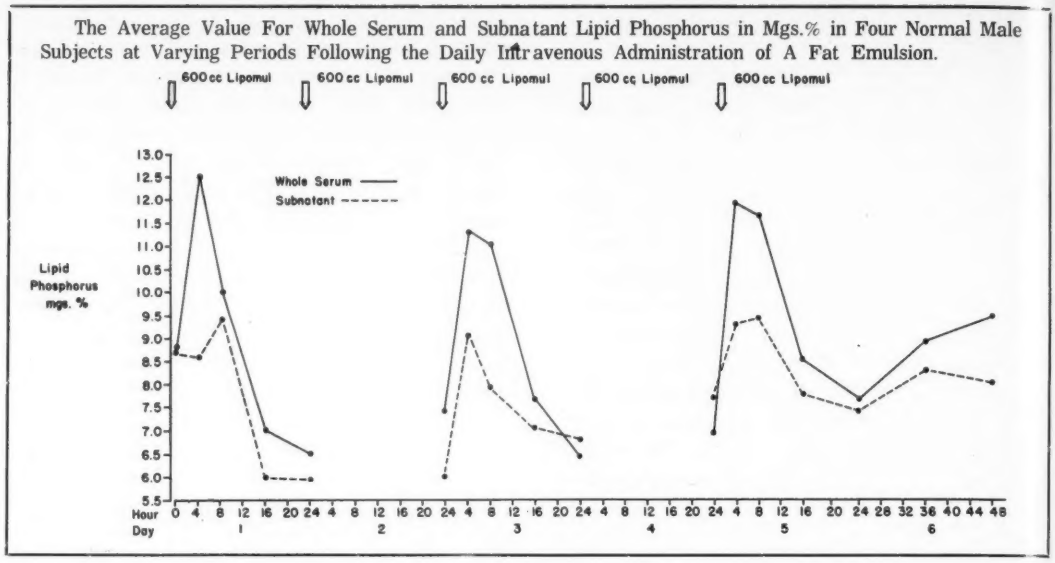
The Average Value For Whole Serum and Subnatant Lipid Phosphorus in Mgs.% in Four Normal Male Subjects at Varying Periods Following the Daily Intravenous Administration of A Fat Emulsion.
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
600 cc Lipomul
Whole Serum
Subnatant
Lipid Phosphorus mgs. %
Hour
Day

Figure 11.

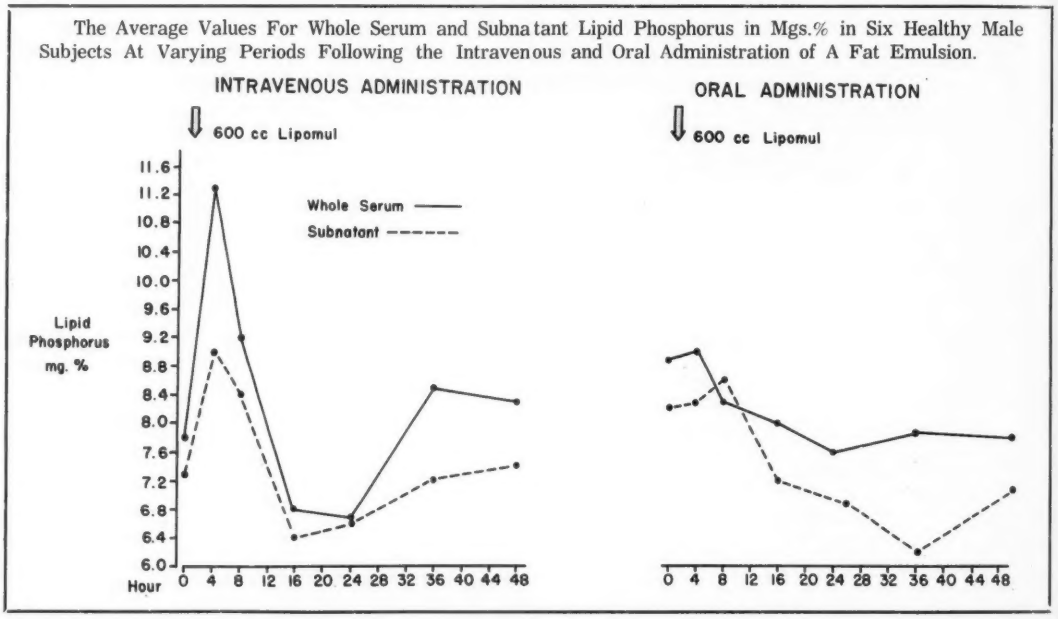
The Average Values For Whole Serum and Subnatant Lipid Phosphorus in Mgs.% in Six Healthy Male Subjects At Varying Periods Following the Intravenous and Oral Administration of A Fat Emulsion.
INTRAVENOUS ADMINISTRATION
ORAL ADMINISTRATION
600 cc Lipomul
600 cc Lipomul
Whole Serum
Subnatant
Lipid Phosphorus mg. %
Hour

Figure 12.

cholesterol in patients receiving multiple infusions over a period of many days. That this should be expected is suggested by the observations in the present study that the changes in cholesterol on the fifth day of the experiment were strikingly different both in quantity and quality than those on the first day. There then appears to be some physiologic adjustment made to the repeated infusions. It would seem, therefore, to us that cholesterol depression by dietary unsaturated fat may involve other mechanisms than those observed in these acute experiments.

Mention has not been made of another important serum lipid; namely, the unesterified fatty acid fraction. Dole[8] and Gordon[9] have suggested that this fraction, which is

combined primarily with albumin, is the form in which the fatty acid is actually carried to the cell for oxidation. In the study performed prior to the present one, unesterified fatty acid in the serum was measured following a single infusion of Lipomul. As would be expected, it rose slightly at the end of the infusion and then promptly returned to normal. This is explicable on the basis of the tremendously rapid turnover of this fraction which has been demonstrated in animals.[16] Presumably this material disappears from the blood almost as rapidly as it enters. Therefore, an elevated level does not develop.

Many questions have been raised and very few answers given by these studies. Obviously much more careful work must be done not only in normals but in abnormals. The use of radioactive labelling technique will be helpful in tracing the pathways of lipid metabolism from the chylomicron to lipoprotein to the cell. It would appear, however, that the serum lipids play a major role in transport mechanisms.

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DISCUSSION

DOCTOR FURMAN: Doctor Mueller, the forced feeding of fat to experimental animals has been reported to produce a syndrome of widespread hemorrhage, including a pancreatitis, and this question asks if there is evidence that the pancreas might be involved in the syndrome which you have reported following lipomul?

DOCTOR MUELLER: We have not done any specific studies on pancreatic function. However, as I recall, Doctor Levenson did some serum amylase studies[1] in his patients which were normal. I can say that clinically there was no suggestion of acute pancreatitis. The pain, although present, was not of a severe nature. There were no abdominal findings which would suggest pancreatitis. I think it is a logical question to ask and probably should be looked at more in the future.

DOCTOR FURMAN: Pulmonary lesions have been reported following intravenous fat emulsion. Are these now being seen with the more recent preparations?

DOCTOR MUELLER: No, they are not.

DOCTOR FURMAN: Doctor Mueller, there is some evidence that clearing, or at least the transport of fat, is related to serum albumin and albumin levels; and furthermore, it has been shown that the degree of postprandial lipemia can be reduced by factors that increase carbohydrate metabolism, such as glucose. Would this suggest that the use of either or both of these agents, namely albumin and glucose, would speed clearing?

DOCTOR MUELLER: Of course there is glucose in the fat emulsion. The fat doesn't exert any osmotic pressure so that glucose must be added for this reason. There is 4 per cent dextrose in the fat emulsion. I don't have any information on the addition of more glucose to the fat emulsion. The question of albumin is an interesting one and one which we looked into a couple of years back. We checked to see what effect the addition of albumin to the fat emulsion might have on the incidence of adverse side effects. This was at the time that we were using the old emulsion and getting high incidence of reactions. Our studies at that time, which have been published,[2] showed that there was no significant change in the incidence of any of the side reactions after the addition of albumin. Unfortunately, at that time we were not studying the clearing mechanism, and I have not looked at that again since that time.

DOCTOR ARTZ: I would like to ask a question. How much intravenous fat emulsion would you give to a patient over a prolonged period and figure you were safe?

DOCTOR FURMAN: Doctor, Mueller, do you want to take that?

DOCTOR MUELLER: No, sir, this is a loaded question. I don't think anyone can answer that at the moment. I have adopted the arbitrary decision that I would stop after 10 injections and then wait awhile. I'm sure this is on the low side. We are at the present time studying one man who has received 32 or 33 infusions and still has not developed any difficulty. I only think, as I said, that people who are planning to use this material for long-term administration ought to be aware that these severe reactions can occur and should be prepared to stop the infusions with the first onset of any peculiarities in a patient. I just don't think we can give an arbitrary figure at this time as to how many infusions will produce this reaction.

DOCTOR FURMAN: Do you give this fat to people who have had myocardial infarcts within the past year?

DOCTOR MUELLER: If there is a clinical indication for it, yes. We have done some other studies using the ballistrocardiogram on persons receiving fat

emulsion. We did a group of normal subjects and then some patients with severe angina. We could detect no adverse effect on the ballistocardiogram during the fat infusion. I know of no incidents of coronary thrombosis that could be attributed unequivocably to the fat emulsion.

DOCTOR FURMAN: Doctor Abbott, do you have anything to add?

DOCTOR ABBOTT: Doctor Mueller's statements that he has an undernourished patient who received fat emulsion intravenoustly for 30 days is of great interest to me. We have given the same emulsion to patients for 12 to 15 days and to one individual for 18 days. We have not seen any of the so-called long-term serious reactions. In every case, the patients had a need for calories and nitrogen. It still makes one wonder if the patients who had serious reactions were not overloaded, especially when they were given 50 to 80 calories and three or more grams of fat per kilogram of body weight per day in a relatively inactive normal individual.

DOCTOR MUELLER: That is, as I said earlier, a very attractive theory. I think it is certainly possible that fat may appear in the tissue before it appears in the blood. The information we have on that is the one liver biopsy we did on this patient at the time she had a reaction. We could not demonstrate any increase of lipid in the liver.

DOCTOR ARTZ: This theory isn't quite so attractive to me. It so happens that we have had three patients on a minimal caloric intake who received large quantities of fat. All were very depleted patients and bled rather profusely. The coagulation times did not go quite as high as Doctor Mueller's patient, in the neighborhood of 24 to 26 minutes. Were your clotting times in silicon tubes?

DOCTOR MUELLER: Ours were siliconized.

DOCTOR ARTZ: This bleeding phenomena did occur in three patients who were depleted individuals on inadequate caloric intakes. However, our infusion of fat was a little more rapid than Doctor Mueller used. We used two infusions of fat a day. There is ample evidence that not all patients bleed because there are two burn patients at the Brooke Army Medical Center who have received 60 units of fat emulsion over a 30-day period with no particular difficulty and no bleeding tendency. It is not every patient that bleeds. Further investigation is necessary.

DOCTOR ABBOTT: I think that fat overloading may still be an important factor in spite of the fact that Doctor Artz says his patients weren't overloaded. I would like to point out that if his debilitated patients weighed 50 kilograms, they were getting from the intravenously administered fat over 3½ grams of fat per kilogram of body weight, which would probably represent more fat per day than an adult could transport and metabolize. We should think in terms of calories or grams of fat per square meter surface area or per kilogram of body weight per day when we are discussing the amount we are giving, **not** in total volume or grams. We have had patients who weighed 40 kilograms and thus on a 1800 caloric diet were getting over 40 calories per kilogram. In most of us who weigh 70 to 80 kilo's, such a caloric intake would represent an inadequate intake. I would also like to emphasize that oral nutritional intakes have to be considered in conjunction with intravenous alimentation. In discussing the fat intake of Doctor Artz's patients, if an oral intake of 50 to 100 or more grams of fat were taken daily, this would increase the total daily fat intake per kilogram of body weight.

DOCTOR FURMAN: Doctor Mueller, can a humoral pyrogenic factor be demonstrated in the blood of patients having a febrile reaction to intravenous fat? And the second question is what is the response of patients with nephrosis to intravenous fat?

DOCTOR MUELLER: That is relatively easy to answer, because I don't know the answer to either one. I don't know of any studies that have been done on the blood of patients receiving intravenous fat which would indicate a pyrogen. Whether or not a pyrogen exists is still open to some question. The fat emulsion itself is pyrogenic as tested in laboratories, according to the standard techniques for testing for pyrogens. Before I will accept the pyrogenic concept of the fever from fat emulsion, future work will have to be done.

I do not have any information on the use in nephrosis. We have used it in patients with uremia, but none with the nephrotic syndrome.

DOCTOR FURMAN: Doctor Mueller, would you care to speculate regarding what role, if any, the lipid mobilizing factors might be playing in these phenomena which you have reported this morning?

DOCTOR MUELLER: This would have to be strictly speculation because I have not had the opportunity to have any of this material to study. This material which has been found in high concentrations, particularly in the urine of horses given large amounts of cortisone, when injected into fasting animals, produces hyperlipemia. It originates from the anterior pituitary and its relationship, for instance, to growth hormones, which can also produce hyperlipemia, is still unclear. I just don't think there is enough information from any source to say whether it plays any role in the clearing of these fat emulsions or not. As I say, this work has been done principally in animals by one group of investigators, to my knowledge.

MEMBER OF THE PANEL: Do you know of any specific electrolyte changes that occur during or following fat emulsion administration?

DOCTOR MUELLER: Yes, this has been studied principally, to my knowledge, by Doctor Becker[3] in Chicago and by the group in Boston also. There is a slight decrease in potassium associated with the intravenous infusion of fat, with no essential change in sodium or in pH or CO_2.

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The Use of Fat Emulsion, Alcohol and Protein Hydrolysates in Surgical Patients

WILLIAM E. ABBOTT
HARVEY KRIEGER
STANLEY LEVY

THERE ARE NUMEROUS FACTORS which influence the metabolic response to operation as measured by the nitrogen, sodium and potassium balance. These include the age and the sex of the patient, the presence or absence of complications, the type and magnitude of the surgical procedure, and the nutrition of the patient. In order to study the effects of nutrition on the metabolic response to surgery it is necessary to remove as many extraneous complicating factors as possible. In the present work we have used only male patients who are undergoing hemigastrectomy in order to reduce the number of variables in the study.

Figure 1 summarizes the data obtained from three patients who were maintained by the intravenous administration of hexose solutions on the day of operation and for at least the next four postoperative days. E.W. received protein hydrolysates on the day of operation. In these and subsequent charts the vertical dotted line represents the day of operation. The areas below the zero line in the water, sodium, potassium and nitrogen balance charts represent the degree of negative balance, while the black areas above the zero line represent positive balance. In the use of the caloric intake the clear areas represent an intravenous intake while the cross hatched areas represent periods of oral diet. All three patients developed large negative nitrogen balances. During the five day period (day of operation and the next four days) the cumulative nitrogen deficits were 57, 70 and 63 gms. for patients E.W., D.B., and M.T. respectively.

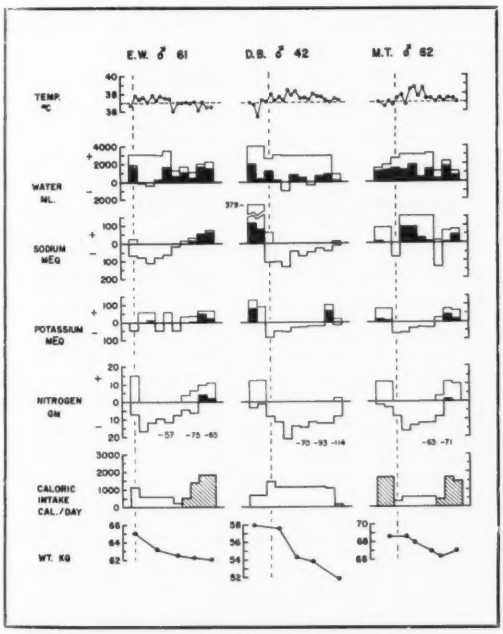

Figure 1. The balance data obtained from the study of three patients undergoing gastrectomy. On the day of operation and for at least the first four postoperative days they were maintained on nitrogen free intravenous regimen which provided 750 to 1000 calories.

The figures listed under the nitrogen balance charts show the cumulative nitrogen balances. Two of the patients (E.W. and M.T.) went into positive nitrogen balance when their caloric and nitrogen intakes increased. During the periods of intravenous feedings these three patients received no nitrogen and usually less than 1000 calories per day. One would not expect a patient who receives no nitrogen to be in anything but negative nitrogen balance. These patients were showing average daily deficits of 7 to 14 gms. of nitrogen during the first five day period on the intravenous regimen. In an earlier study[1] it was shown that normal non-operative male subjects maintained on an oral diet similar in caloric and nitrogen content developed a daily nitrogen deficit of approximately 7 gm. Calloway and Spector[2] have also reported that individuals on diets devoid of nitrogen and receiving 750 or more calories per day were in negative balance to the extent of 7 to 8 gms. per day. They also reported that with smaller caloric intakes greater nitrogen deficits occurred. These three postoperative patients showed nitrogen deficits similar to or a little greater than one would expect in non-operative patients maintained on comparable regimens. During the time the patients were in negative nitrogen balance D.B. and M.T. who received no potassium were also in negative potassium balance. The potassium bal-

ance of E.W. varied depending on his intake of potassium. When patients D.B. and M.T. were given potassium they immediately went into positive potassium balance. Patient D.B. who had the largest nitrogen deficit also had the greatest change in body weight (6 kg.) although the other two patients had lost weight to the extent of 2 to 3 kg.

Figure 1 illustrates that the patients who were maintained on intravenous regimens consisting only of hexose solutions with or without added electrolytes developed large nitrogen deficits. Such regimens are devoid of nitrogen and deficient in calories offering usually less than 1000 calories per day. With such an abnormal nutritional intake the patients lost between 3 to 5 kg. of body weight during the course of the study. With the development of various nutritional products (protein hydrolysates, fat emulsions, etc.) suitable for intravenous administration it is no longer necessary to maintain the postoperative patient on a starvation regimen.

Figure 2 summarizes the data obtained from three patients who were maintained during their postoperative periods on intravenous regimens consisting of protein

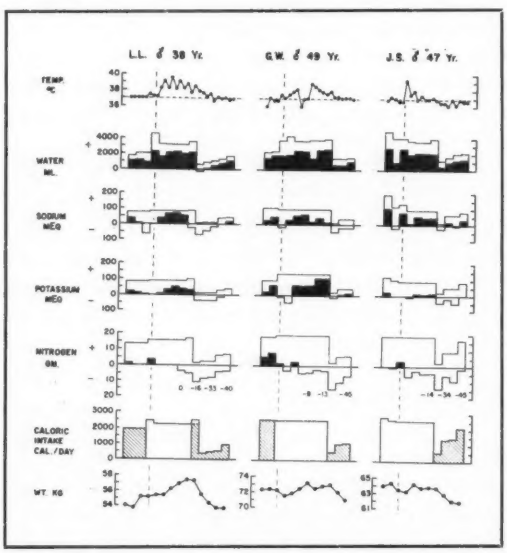

Figure 2. The balance data are shown from the study of three patients who had gastrectomies. The day of operation and at least the first four postoperative days these patients were maintained on intravenous regimens which provided 12 to 18 grams of nitrogen and 2500 calories.

hydrolysates containing sugar and electrolytes. They were also given a fat emulsion as a source of extra calories. With such a regimen it is possible to give between 15 and 18 grams of nitrogen (equivalent to 93 to 100 gm. of protein) and 2500 or more calories per day. During the five day period consisting of day of operation plus the first four postoperative days, patient L.L. showed a cumulative nitrogen deficit of 0.5 gm., G.W. 13 gm. and J.S. 14 gm. It should be noted that larger nitrogen deficits developed when the patients were switched from the high caloric, high nitrogen intravenous regimen to an oral diet which was lower in nitrogen and calories. Usually the reason for the development of these deficits was that the intake of nutrients was not adequate to maintain nitrogen equilibrium when the patients were first switched to an oral diet.

It should be also noted that these patients were retaining potassium during the immediate postoperative period. During this time they were receiving 100 to 120 mEq. of potassium per day. Patent L.L. had the minimal (0.5 gm) five day cumulative nitrogen deficit postoperatively in spite of the fact that he developed a fever which reached 40°C at times. One would normally expect that a fever would cause an increased breakdown of body tissue and an increased nitrogen deficit.

During the period of intravenous feedings these patients either maintained their body weight or gained small amounts. Part of this gain could be attributed to the retention of both sodium and water.

From the data presented in Figure 2 one might conclude that following major surgery (e.g., gastric resection) that patients need not show large nitrogen and potassium deficits. In earlier studies[1,3] we have shown that the nitrogen deficit in a postoperative patient is dependent upon the nitrogen and caloric intake. With increasing amounts of calories and nitrogen the patients show smaller nitrogen deficits. Giving 12 to 18 gm. of nitrogen by the parenteral route is a simple procedure with the modern protein hydrolysates but attaining an adequate ca-

loric intake by this route is difficult in all but patients of small stature if one does not employ fat emulsions. It has been shown[4] that the dog utilizes intravenosly administered fat emulsions as well as orally administered fat. It has also been noted[5] that traumatized (multiple fractures of one leg) rats do not handle intravenously administered fat in a manner different than that which occurs in the normal rat. By increasing the carbohydrate content of protein hydrolysates it is possible to increase the caloric content. But increasing the carbohydrate content beyond about 12½ per cent renders the solutions too hypertonic to be used without extreme precautions (very slow administration in large veins, etc.). The caloric content of an intravenous regimen may also be increased by adding alcohol solutions to protein hydrolysates. Patient R.R. was given a 5 per cent protein hydrolysate which contains 12.5 per cent fructose and 2.4 per cent alcohol. Each liter of this solution provides 800 calories.

There are reports in the literature[6, 7, 8] which indicates that the anabolic hormone testosterone and its derivatives tend to produce positive nitrogen balance in postoperative patients being maintained on adequate amounts of nitrogen but suboptimal caloric intakes. Figure 3 indicates data obtained from three different individuals who had a subtotal gastric resection. They were maintained on intravenous regimens for at least the day of operation and the first four postoperative days. In some cases the patients received intravenous alimentation preoperatively. They had nitrogen intakes of 12 to 18 gm. per day and caloric intakes ranging between 2200 and 2500 calories per day. In addition each patient received a day or two preoperatively 250 mg. of a long acting testosterone derivative, depo-nortestosterone or depo-testosterone. These individuals showed cumulative nitrogen balances of from -15 to +10 gm. for the five day period of study. Again it may be noted that when patients C.N. and R.R. were switched to an oral diet they developed larger cumulative nitrogen deficits than those which occurred during the immediate postoperative period. This was due to the fact that both their caloric and nitrogen intakes were too low to maintain nitrogen equilibrium during the initial oral feedings. It cannot be definitely decided from these studies whether or not the anabolic hormone produces a substantial reduction in the nitrogen deficit in patients receiving adequate amounts of calories and nitrogen. The increased caloric intake in these patients was produced by administering protein hydrolysates containing carbohydrate and a fat emulsion. During the immediate postoperative period the patients showed either very little change in body weight or actually a gain. The weight gain exhibited by these patients is due primarily to the retention of sodium and water.

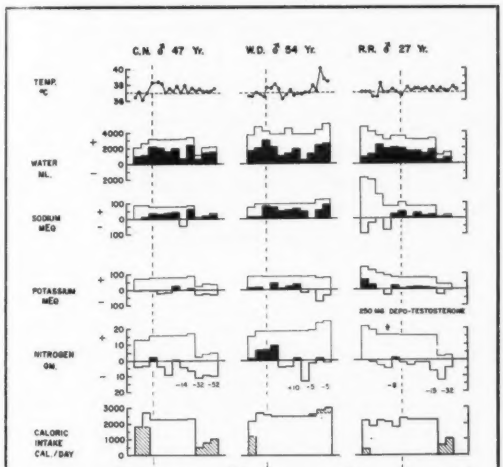

Figure 3. The balance data obtained from the study of three patients who had gastrectomies. They were given an injection of a long acting testosterone derivative 1 to 2 days preoperatively. C.W. and W.D. received 250 mg. of depo-nortestosterone cyclopentylpropionate and R.R. depo-testosterone.

The studies shown in the preceding three figures were carried out in postoperative patients who did not have complications. It is our belief that postoperative complications, e.g., hemorrhage, infection, atelectasis, etc., may cause greater nitrogen deficits than the operative trauma. Figure 4 shows the data obtained from the study of two patients who had postoperative complications. Patient F.R. had postoperative hemorrhage and pneumonitis. During the day of operation and the next four postoperative days, he developed a cumulative nitrogen

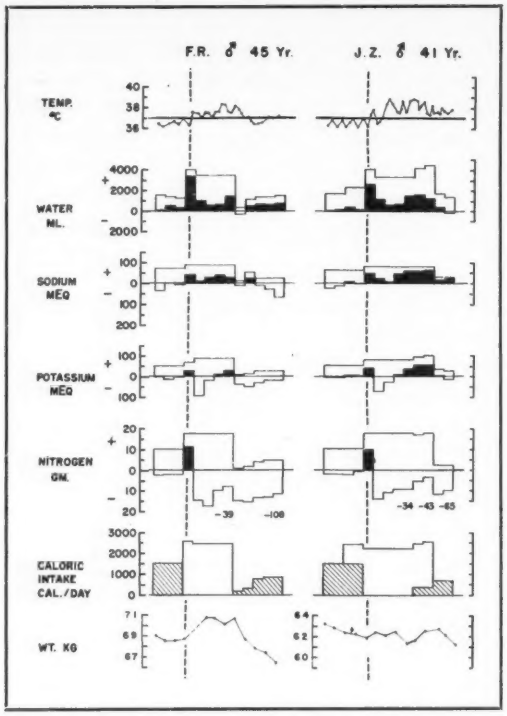

Figure 4. Shown are the balance data obtained from the study of two patients maintained on nutritionally good intravenous regimens postoperatively but developed complications.

deficit of 39 gm. in spite of receiving 2500 calories and about 18 gm. of nitrogen daily. J.Z. had a wound infection, atelectasis, and showed a 34 gm. postoperative five day cumulative nitrogen deficit in spite of an excellent nitrogen and caloric intake. Both of these patients showed large cumulative nitrogen deficits when they were switched to oral regimens. The nitrogen deficits of these patients should be compared with those in the previous two figures. From the present work and earlier studies it might be concluded that the major portion of the nitrogen deficit which occurs postoperatively in the uncomplicated case is due to the poor nutritional intake with which the patient is provided.

It has been shown definitely that the nitrogen and potassium deficits which occur in postoperative patients can be minimized or even negated by adequate nutrition during the pre and postoperative periods. However, one cannot show by the usual criteria that the patient is clinically better because he received a nutritionally adequate regimen postoperatively. By the same token it has never been demonstrated that starvation per se is advantageous. On the other hand it is well known that adequate nutrition during the pre and postoperative periods can reduce the morbidity and mortality rates of debilitated and malnourished surgical patients.

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DISCUSSION

DOCTOR FURMAN: Doctor Abbott, in any given patient, how do you decide what portion of the day's caloric intake shall be derived from fat, protein, or carbohydrate, or should it be mainly from one?

DOCTOR ABBOTT: Before answering your question I would like to say that reports from good laboratories have indicated that nitrogen was not spared in patients who were given a fat emulsion intravenously postoperatively. However, in these studies the patient did not get any nitrogen; obviously, it can't be spared if none is given. We have given 2,000 nitrogen-free calories to patients who weighed 50 or 60 kilograms and they waste nitrogen to about the same extent that they would if they had been given only 400 to 800 calories. It is obvious, first of all, as far as nitrogen balance and good nutrition is concerned, that you need protein. We feel that protein should make up about 20 to 25 per cent of the total caloric intake in adult patients following injury or in the postoperative state. I think everyone agrees a little higher intake of protein is probably desirable in patients who are repairing damaged tissues. As to the other source of calories, we feel that sugar is readily available for energy utilization and fat more slowly utilized, so that we prefer to give about half the non-protein calories as carbohydrate and the remainder as fat. This means fewer grams in the form of fat are taken since one gram of fat supplies nine calories to only four calories for a gram of sugar. We have not done any studies in patients who were maintained on a diet totally made up of just protein and fat. Actually, as Doctor Mueller has emphasized, we could not do this with the present fat emulsion because four or five per cent sugar is contained in the available emulsions.

DOCTOR FURMAN: Do you hesitate to infuse protein hydrolysates if there is any degree of uremia or renal insufficiency?

DOCTOR ABBOTT: I think if there is a renal shut-down, that a very minimal intake of nitrogen or a zero nitrogen intake is probably desirable. There have been studies by Doctor Ole Malm, now at Walter Reed Hospital and formerly from Oslo, Norway, in patients who had a renal shut-down which showed that two to three gram intakes of nitrogen per day did not exceed the wear and tear nitrogen and thus such an amount was well tolerated. Anything above that would probably not be desirable. We believe that two or three liters of the protein hydrolysates are indicated (which would provide 12.5 to 18 grams of nitrogen) in adult patients who have fairly good liver and kidney function. Again, I think it should be emphasized that in the patients with severe liver disease, a high intake of protein may produce hepatic coma and serious effects.

DOCTOR FURMAN: Does the over-all nitrogen balance appreciably influence wound healing? How much may one speed recovery by maintaining the nitrogen balance strongly on the positive side?

DOCTOR ABBOTT: I believe that when there is marked protein depletion there is interference with wound healing. However, the wound seems to get priority in the utilization of proteins. Studies have been done which indicate that proteins will even be taken from muscle and liver to heal a wound. Doctor Carl Moyer and his group did some interesting studies in burned rats. They gave comparable caloric intakes with very low nitrogen intakes to some animals and good protein intakes to others, and the rate of wound healing after a standard burn was essentially the same. However, after 60 to 70 days, when the wounds were healed, the animals were autopsied and marked fat infiltration of the liver, or cirrhosis, was evident in the animals who had the low protein intake while the other animals apparently had normal livers. I believe that it is hard in this day and age, when we have minimal losses and apparently well-nourished patients to operate upon, to note any great difference. However, many years ago, during Napoleon's time when the Russians and French were fighting, the Russian Army was given vodka and good quantities of meat in their diets and their injured soldiers had a much lower mortality and morbidity rate that the other armies reported. On further study, it was found that when the caloric and nitrogen intakes in this latter group were tabulated, the injured men had poor nutritional intakes. So I think there is a relationship, but it is certainly not apparent in the well-nourished patient who had minimal difficulties.

DOCTOR FURMAN: What is the metabolic effect of alcohol? Is it all utilized calorically? What is the caloric value of alcohol? Is it the same as sugar?

DOCTOR ABBOTT: I believe that alcohol is utilized primarily for energy, although it may be metabolized and converted into sugars and fats within the body. The caloric value is around six to seven calories per gram of alcohol, four per gram of sugar and protein, and around nine calories per gram of fat.

DOCTOR FURMAN: Is not the problem with alcohol the question of the rate of administration?

DOCTOR ABBOTT: It has to be given relatively slowly to prevent side effects, and this limits one as to how many calories they can give from alcohol in 24 hours. We use only a two and a half to three and a half per cent alcohol solution and govern the rate of administration more by the sugar content rather than the amount of alcohol, so that we get little or no spillage of sugar into the urine. We have not noted any ill effects from alcohol and in many instances most of the patients have not known that they had been given it. As I stated, we govern our rates of infusion by the carbohydrate content of the solution and size of the patient because this is the nutrient most apt to be spilled in the urine. We try to give it at a rate not faster than 0.5 to 0.7 gm. of sugar per kilogram of body weight per hour. It can be given a little faster (0.85 gm per kil. per hour) in non-traumatized, afebrile patients.

PRESIDENT'S LETTER

In this first effort at composing a President's Letter, I wish to express my appreciation and admiration for the calm, rational manner in which this office has been administered during the past year by Alfred T. Baker, M.D., of Durant. Many of the Council and Committee appointments will be carry-overs of men carefully selected by Doctor Baker. Much of the work to be done will be a continuance of efforts in the direction which he has indicated for us in the past year. His counsel will be asked in all important matters of policy decision for this organization.

The Oklahoma City meeting, May 2, 3, and 4, was certainly one of our very best State Meetings, and Doctor Charles Bielstein and Doctor Bert Keltz with their committee members can take real pride in the smooth functioning of all sections of this meeting.

The Association is in good shape. We own our own home debt free and have money in the bank. Operations have been kept within the budget successfully for the past several years. There are 1568 active, dues paying members, with an additional 125 Life and Honorary Members. We have 60 more doctor members than in 1959. Our Headquarters Staff is one of the best in the nation. The organization is run for doctors and by doctors. We're going ahead.

Walter E. Brown, M.D.

Walter E. Brown, M.D.
President

The first specific aldosterone-blocking agent...

ALDACTONE™

effectively extends the medical control of edema or ascites.

It introduces a new therapeutic principle in the treatment of...

CONGESTIVE HEART FAILURE • HEPATIC CIRRHOSIS
THE NEPHROTIC SYNDROME • IDIOPATHIC EDEMA

ALDACTONE introduces a new class of therapeutic agent, the aldosterone-blocking agent providing:

satisfactory relief of resistant or advanced edema even when all other agents, alone or in combination, are ineffective or are only partially effective.

A New Order of Therapeutic Activity

ALDACTONE acts by blocking the effect of aldosterone, the principal mineralocorticoid governing the reabsorption of sodium and water in the distal segment of the renal tubules.

By so doing Aldactone establishes a fundamentally new and effective approach to the control of edema or ascites, including edema resistant or unresponsive to conventional diuretic agents.

Further, because of its different site and mode of action in the renal tubules, Aldactone has a true, highly valuable synergistic activity when used with a mercurial or thiazide diuretic.

What Physicians May Expect of Aldactone

It is fully expected that Aldactone will change present medical concepts of the therapeutic limitations of managing edema. Many patients living in a greater or lesser state of edematous invalidism can now be edema-free. To others, gravely ill, Aldactone will be life-saving.

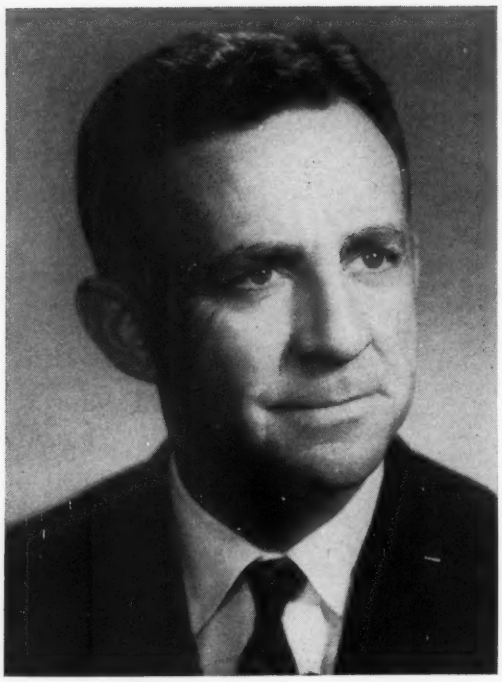
When used alone, Aldactone will produce a satisfactory diuresis in about half of those patients whose edema is resistant to conventional diuretic agents.

When Aldactone is used in a comprehensive therapeutic regimen, which includes a mercurial or a thiazide diuretic, a satisfactory diuresis and relief of edema may be expected in approximately 85 per cent of edematous patients *who would not otherwise respond.*

DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 100 mg. four times daily. Aldactone should be administered for at least four or five days before appraising the initial response, since the onset of therapeutic effect is gradual when it is used alone. Aldactone manifests accelerated activity with greater response as early as the first and second days when used in combination with a mercurial or thiazide diuretic.

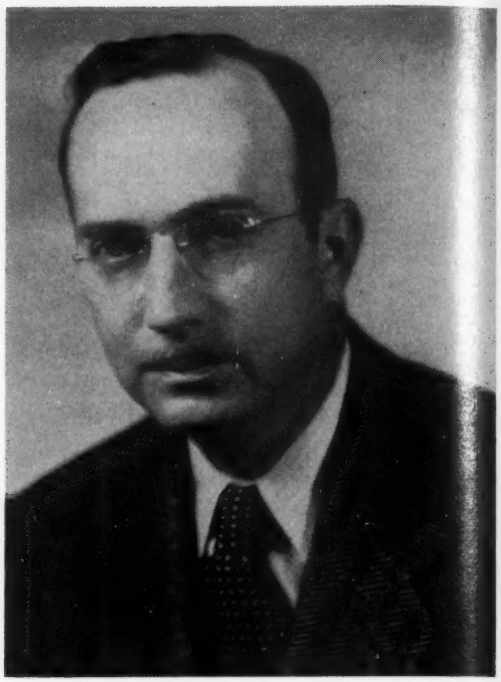
SUPPLIED: Aldactone is supplied as compression-coated yellow tablets of 100 mg.

G. D. SEARLE & CO.
Chicago 80, Illinois
Research in the Service of Medicine



WALTER E. BROWN, M.D.
President

Walter E. Brown, M.D., a native Tulsan, graduated from Washington University School of Medicine in St. Louis in 1935, following which he served rotating internships at the Kansas City General Hospital and the State University Hospital in Oklahoma City. He was Assistant Radiologist at St. John's Hospital in Tulsa in 1937-38, and then accepted an appointment as Graduate Assistant in Radiology at the Massachusetts General Hospital in Boston. He served as radiologist to the 167th General Hospital in the ETO during World War II and has practiced his specialty of radiology in Tulsa since his return from military service in November of 1945. Doctor Brown is a Diplomate of the American Board of Radiology and a Fellow of the American College of Radiology. He served as Delegate to the State Medical Association from Tulsa County for five years, has been Secretary-Treasurer of his Society, and was Vice-President of the Tulsa County Society last year. He has held varied committee assignments in the State Medical Association, including the chairmanship of the Medicare Committee.



CLINTON GALLAHER, M.D.
President-Elect

Another seasoned member of the OSMA was elected to succeed Doctor Brown in 1961. Clinton Gallaher, M.D., Shawnee, graduated from Northwestern University Medical School in 1929, after receiving pre-med training and two years' medical education at the University of Oklahoma. He subsequently interned at Buffalo General Hospital and established a general practice in Shawnee before returning to Chicago for a residency in E.E.N.T.

In 1937, he established an E.E.N.T. practice in Shawnee and began a long career of service to his community and profession. He has been an OSMA Councilor for twelve years, a member of the Oklahoma Board of Medical Examiners for twelve years and Speaker of the House of Delegates for eight years. In his own county, he has served as President and Secretary of the local medical society.

Among other professional honors is his membership in the American College of Surgeons.

Seven Hundred Attend 54th Annual Meeting

The OSMA's 54th Annual Meeting provided a fitting climax to another successful year of association activities. More than seven hundred physician members registered for the meeting; attending the scientific lectures as well as the many related events which are traditionally offered. C. M. Bielein, M.D. and Bert Keltz, M.D., served as General Chairman and Scientific Works Chairman, respectively.

Scientific activities were held in Oklahoma City's Municipal Auditorium, on May 2, 3 and 4. They were preceded on April 30 and May 1 by business meetings of the Council and House of Delegates.

Business Activities

New officers elected during the House of Delegates meeting are: Clinton Gallaher, M.D., Shawnee, President-Elect; J. Hoyle Carlock, M.D., Ardmore, Vice President; Mark R. Johnson, M.D., Oklahoma City, Secretary-Treasurer; Marshall O. Hart, M.D., Tulsa, Speaker of the House of Delegates; and, C. M. Hodgson, M.D., Kingfisher, Vice Speaker of the House of Delegates. Wilkie D. Hoover, M.D., Tulsa, and Joe L. Duer, M.D., Woodward, succeeded themselves as Delegate and Alternate to the American Medical Association.

In other actions, the House of Delegates:

- Approved the report of the Council on Professional Education which proposed an extensive postgraduate education program to be jointly sponsored by the OSMA and the University of Oklahoma School of Medicine.
- Heard without comment the report of the Council on Insurance, which significantly announced a forthcoming rate increase in professional liability insurance.
- Approved parts of the Council on Public Health Report, which delineated association responsibilities in providing health care for the aged at the state and local levels.
- Amended the Constitution and By-Laws to the extent that the removal of a physician's narcotic permit does not automatically result in the termination of OSMA membership. Disciplinary decision will rest with Council.
- Commended Grady F. Mathews, M.D., for his years of service as Commissioner of Health.
- Re-affirmed opposition to compulsory Social Security for physicians.
- Re-affirmed opposition to Forand-type legislation and announced opposition to legislative compromise in providing health care for the aged through taxation.
- Rejected a resolution calling for the resumption of a contractural agreement between the OSMA and the Medicare Program.

PRESIDENTIAL APPOINTEES, 1960-1961*

EXECUTIVE COMMITTEE

Walter E. Brown, M.D. — Tulsa	J. Hoyle Carlock, M.D. — Ardmore
Alfred T. Baker, M.D. — Durant	R. Q. Goodwin, M.D. — Oklahoma City
Clinton Gallaher, M.D. — Shawnee	Joe L. Duer, M.D. — Woodward

CHAIRMEN OF COUNCILS

Public Policy
J. R. Stacy, M.D., Oklahoma City

Insurance
Bruce R. Hinson, M.D., Enid

Socio-Economic Activities
Mark R. Johnson, M.D., Oklahoma City

Professional Education
R. R. Hannas, Jr., M.D., Sentinel

Public Health
Bert T. Brundage, M.D. Thomas

*Complete committee appointments will appear in a later issue of the Journal

Vice Speaker J. Hoyle Carlock, M.D., presides at the House of Delegates meeting

• Opposed H.J.R. 517, a proposed constitutional amendment which would permit Oklahoma to become indebted up to $35.5 million to provide capital funds for higher education.

• Referred for further study to the Council on Professional Education a resolution which recommended the creation of a scholarship fund for medical students.

• Passed a resolution which provided that the OSMA take an active, non-partisan part in local, state and national government, particularly in regard to the selection of qualified candidates for office.

Inaugural Ball

On Tuesday evening, Walter E. Brown, M.D., Tulsa radiologist, succeeded Alfred T. Baker, M.D., Durant, as President of the Oklahoma State Medical Association. The inaugural ceremonies were followed by dancing to the music of Paul Neighbors and his orchestra. Some 350 physicians and their attended the evening's activities.

In his remarks to the group, Doctor Baker paid tribute to the cooperation he had received during his term of office and expressed gratitude for the honor that had been bestowed upon him.

Doctor Brown presented himself with a personal challenge to live up to the standards set by his predecessors and, despite, today's grave problems, voiced optimism for the ability of organized medicine to continue its progress.

The Scientific Program

Fifteen outstanding guest speakers drew maximum audiences at general sessions held in the Zebra Room of the Municipal Auditorium. Highlighting the program were panel discussions on vascular disease, perinatal mortality and rehabilitation.

The latter portion of the program was attended by nearly two hundred physicians, physical and occupational therapists, as well as by Senators and Representatives of the State Legislative Committee on Rehabilitation. In addition, a Roundtable Luncheon on Monday was well attended, as was the Tuesday Luncheon featuring a presentation entitled "How Public Opinion Can Socialize a Profession or Industry." The OSMA hosted O.U.'s senior medical class at the Tuesday event.

One hundred technical and scientific exhibits completed the well-balanced program. In the field of scientific exhibits, committee chairman Edward R. Munnell, M.D., presented awards to the following: Scientific

Exhibit: 1st place, Joseph W. Kelso, M.D. and Joseph W. Funnell, M.D.; 2nd place, Ethan Allen Walker, Jr., M.D.; 3rd place, Averill Stowell, M.D. "Klinical Kaleidoscope" (bizarre cases): 1st place, R. Kent Alexander, M.D.; 2nd place, Samuel M. Glasser, M.D. and Rene B. Menguy, M.D.,; 3rd place, J. Neill Lysaught, M.D.

Complementing the OSMA program were nine specialty society meetings, the majority of which were held on Monday evening during the state meeting. Guest speakers for the OSMA program also appeared before the specialty groups.

Record-Breaking Golf Tournament

Three records fell during the annual golf tournament which was held at Twin Hills Country Club under the direction of Peter E. Russo, M.D. In the first place, the seventy-six registrants made it the largest contest in OSMA history; secondly, the low gross trophy was won with an even par score; and, lastly, a hole in one was scored by A. C. Lisle, M.D., Oklahoma City.

Trophy winners were: Edmond H. Kalmon, M.D., Oklahoma City—Low Gross (71); Lester Moline, M.D., Lawton—Handicap (65); Averill Stowell, M.D., Tulsa, Birdie Trophy (3); A. C. Lisle, M.D., Oklahoma City—Low Hole (hole in one); C. E. Woodard, M.D., Drumright—High Score (137); and, John W. Records, M.D., Oklahoma City—High Hole Score (12). In addition to the trophy winners, eight physicians made scores of 80 or less.

Woman's Auxiliary Meeting

Oklahoma medicine's right arm, the Woman's Auxiliary, held a concurrent meeting at the Skirvin Hotel to review last year's achievements and lay plans for the succeeding year. Mrs. Clifford M. Bassett, Cushing, turned over the auxiliary reins to Mrs. Virgil Ray Forester, Oklahoma City, and Mrs. W. P. Fite, Sr., Muskogee, was named as President-Elect.

Other officers elected were: Mrs. Milton L. Berg, Tulsa, 1st Vice President; Mrs. T. A. Ragan, Norman, 2nd Vice President; Mrs. C. W. Freeman, Oklahoma City, Secretary; Mrs. John W. Records, Oklahoma City, Treasurer; and Mrs. Louis S. Frank, Oklahoma City, Treasurer-Elect.

The 109th Annual A.M.A. Meeting: A Forum for 2,000 Top Medical Men

The 109th annual meeting of the American Medical Association will be a forum presented by some of the nation's top scientific brains.

Approximately 2,000 physicians, all outstanding in their field, will participate in presenting the scientific program of the meeting to be held in Miami Beach, June 13-17.

There will be two general scientific meetings in the Grand Ballroom of the Fontainebleau Hotel, and other lectures, symposiums, and panel discussions in the Fontainebleau, Eden Roc Hotel, and in the new, air-conditioned Miami Beach Exhibition Hall. Sessions on dermatology, being held jointly with the Society for Investigative Dermatology, will be in the di Lido Hotel.

The opening general scientific meeting, Monday afternoon, June 13, will begin with the Joseph Goldberger Lecture on Clinical Nutrition. Dr. Carl A. Lincke, chairman of the A.M.A. Council on Scientific Assembly, will preside at this meeting.

The lecture will be followed by a symposium on nutrition, including an address by Grace A. Goldsmith, professor of medicine, Tulane University School of Medicine, New Orleans, on "Highlights on the Cholesterol—Fats, Diets and the Atherosclerosis Problem."

The second general meeting will be a symposium on "Evaluation and Preparation of Patients for Anesthesia and Surgery," Tuesday morning, June 14, to which the sections on Anesthesiology, Diseases of the Chest, General Practice, Internal Medicine, Pediatrics, Pathology and Physiology, and Surgery have contributed. Participating will be Meyer Saklad, Providence, R.I.; Thomas Rardin, Columbus, Ohio; Eugene Turrell, Milwaukee, Wis.; John S. LaDue, New York City; Arlie R. Mansberger, Jr., Baltimore; George Meneeley, Nashville, Tenn.; Robert M. Smith, Boston and C. Rollins Hanlon, St. Louis, Mo.

Section Programs

What's new in surgery will be explored during a symposium and panel discussion on Wednesday morning. The program was developed from suggestions obtained from a survey of the heads of departments of surgery in the nation's medical schools.

The symposium will be on "Recent Advances in Treatment of the Cancer Patient" with an introduction to the problem including methods of decreasing spread of cancer cells during operations being presented by Warren H. Cole, Chicago. Doctor Cole also will serve as moderator of the panel on "Current Status of the Treatment of Advanced Cancer of the Thyroid and Breast."

Arthur M. Master, New York City, will speak on "Effort, Occupation (including physicians) in Coronary Occlusion" during a symposium on Medical Chest Emergencies, and John F. Briggs, St. Paul, Minnesota, will discuss "Pulmonary Embolism."

John H. Moyer, Philadelphia, will moderate a symposium on "Edema—Its Physiology and Use of Newer Diuretics in Its Treatment." Irving S. Wright, New York, will moderate a symposium on "Pathogenesis and Treatment of Thrombo-embolic Phenomena." Daniel C. Moore, Seattle, Washington, will take part in a session on "Newer Trends in Diagnosis and Treatment" discussing "Oxygen—The Rational Therapy for Systemic Toxic Reactions from Local Anesthetic Drugs."

There will be panel discussions on "Tumors of the Trachea and Bronchial Tree," with Paul H. Holinger, Chicago, moderator, and one on "Disseminated Diseases of the Chest," with Harold O. Peterson, Minneapolis, moderator.

Highlights of other section meetings include:

Nervous and Mental Diseases—E. S. Gurdjian, Detroit, "Critique of Occlusive Disease of the Carotid Artery and the Stroke Syndrome." Leo H. Bartemeier, Baltimore, "Comments on the Relations Between Psychiatrists and Other Physicians."

Obstetrics and Gynecology—Stirling G. Pillsbury, Long Beach, California, "31,5[illegible]5 Deliveries with One Maternal Death." Jerome M. Kummer, Santa Monica, California, "An Answer for Criminal Abortion."

Internal Medicine—"Symposium on Hypocholesteremic Drugs." Walter L. Palmer, Chicago, "The Billings Lecture: Causality in Peptic Ulcer." Rudolph H. Kampmeier, Nashville, Tennessee, "Collagen Diseases—Some Unanswered Questions."

Laryngology, Otology, and Rhinology—George A. Sisson, Syracuse, New York, "Problems and Complications in Head and Neck Surgery." C. M. Kos, Iowa City, Iowa, "Five Year Results of Stapes Mobilization and Current Results with Vein Plug Stapedeoplasty."

Preventive Medicine—Jan H. Tillisch, Rochester, Minnesota, "Medical Aspects of Safety in the Air." Robert B. Stonehill, San Antonio, Texas, "Air Travel and the Cardiopulmonary Patient," a film presentation.

Orthopedic Surgery—Sidney Keats, Newark, New Jersey, "Surgery of the Extremities in the Treatment of Cerebral Palsy." H. R. McCarroll, St. Louis, Missouri, "The Management of Complicated Ununited Fractures of the Tibia and Fibula."

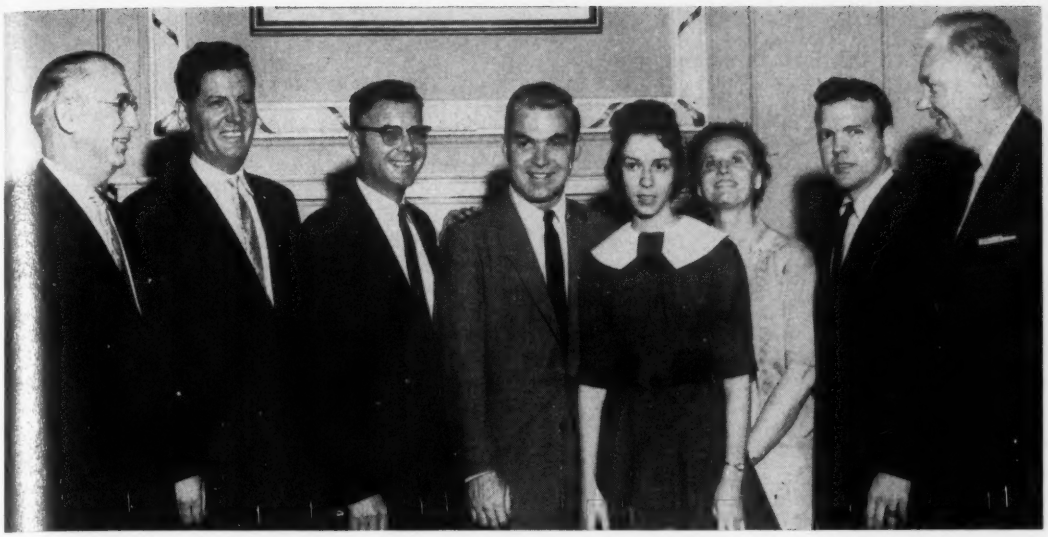
Pediatrics—Leonard S. Sommer, Miami, moderator, "Symposium on Congenital Heart Disease—Present-day Status from Viewpoint of Practitioner of Medicine."

The section on Miscellaneous Topics will feature a half-day session on the "Management of the Older Patient." Participants include Philip Thorek, Chicago.

Exhibits Number 290

About 290 exhibits will be on display in the Miami Beach Exhibition Hall, representing the most outstanding exhibits selected from 540 applications.

A new special exhibit on Body Fluid Disturbances, offering a complete course in body fluids, will be presented in its entirety on two days. Different aspects will begin at specific times to permit physicians to attend only those parts in which they are particularly interested.



Pictured with Miss Mamie Richardson, first place winner of the Governor's Committee on Employment of the Handicapped essay contest are (left to right) Alfred T. Baker M.D., President of the Oklahoma State Medical Association, Durant; Len Yarborough, Executive Vice-President of the AFL-CIO, Tulsa; Roy Tillman, President of the AFL-CIO, Oklahoma City; Governor Edmondson; Miss Richardson; Mrs. Irene Mitchell, teacher of the first-place winner, Ringling; Lt. Governor Nigh; and James Reinmiller, President of the Oklahoma Association of Insurance Agents, Hobart.

Ringling Student Wins Governor's Essay Contest

Miss Mamie Richardson, senior at Ringling High School, placed first in the state essay contest, sponsored by the Governor's Committee on Employment of the Handicapped. More than 4,500 students wrote essays on "Jobs for the Handicapped—Passports to Dignity." Governor J. Howard Edmondson, Lt. Governor George Nigh, and members of the Governor's Committee met with the 10 state essay winners in the Blue Room of the state capitol, where Mamie and other winners were presented their awards.

Mamie received an expense-paid trip to Washington, D.C., to attend the meeting of the President's Committee, May 5-6. This annual award was presented by Len Yarborough of the Oklahoma AFL-CIO. Mr. James Reinmiller, President of the Oklahoma Association of Insurance Agents, presented a $200 savings bond. Mamie will also receive a two-year tuition and fee scholarship from Southeastern State College in Durant.

Mrs. Irene E. Mitchell, teacher of the first-place winner, received an expense-paid trip to accompany Mamie to Washington from Doctor Alfred T. Baker, President, Oklahoma State Medical Association, and a plaque from Lt. Governor George Nigh, which was sponsored by the employees of the Oklahoma City Goodwill Industries.

Shown congratulating Mrs. Irene Mitchell, teacher of the award winner, are Alfred T. Baker M.D., President of the Oklahoma State Medical Association, Durant (left), and Dick Graham, Executive Secretary, Oklahoma State Medical Association.

Carcinoma of the Skin Subject for May Symposium

Carcinoma of the Skin will be the subject of the Sixth Annual Surgery, Radiology, Pathology Symposium to be held May 27-28, 1960 in the auditorium of the University of Oklahoma Medical Center. Sponsored by the Office of Postgraduate Education, University of Oklahoma Medical Center, the Oklahoma Association of Pathologists, the Oklahoma State Radiological Society and the Oklahoma Chapter of the American College of Surgeons, the symposium will afford physicians two days of lectures, round table discussions and case presentations.

A group of specialists has been selected to attract the attention of surgeons, dermatologists, radiologists, pathologists and others interested in carcinoma of the skin problems. Guest speakers will include: Stephen R. Lewis, M.D., plastic surgeon, Galveston, Texas; Charles L. Martin, M.D., radiologist, Dallas, Texas; George T. Pack, M.D., neoplastic surgeon, New York City; Jose M. Sala, M.D., radiologist, Columbia, Missouri; Danely P. Slaughter, M.D., surgeon, Chicago, Illinois and J. Leslie Smith, M.D., pathologist, Houston, Texas.

A complete program follows:

FRIDAY, MAY 27 AND SATURDAY, MAY 28, 1960

FRIDAY MORNING, MAY 27

8:00 a.m. Registration

8:40 a.m. INTRODUCTION
John A. Schilling, M.D.

8:45 a.m. BENIGN AND PSEUDO-NEOPLASMS OF THE SKIN
Lymphoid tumors—hemangiomas of the skin
Lesions previously classified as malignant
Problems in histologic diagnosis and prognostic evaluation
J. Leslie Smith, Jr., M.D.

9:40 a.m. PRECANCEROUS LESIONS OF THE SKIN
Stephen R. Lewis, M.D.

10:10 a.m. Intermission

10:30 a.m. PRINCIPLES OF DIAGNOSIS OF SKIN TUMORS
Clinical evaluation on physical examination
Diagnostic maneuvers
Biopsy techniques and principles
Danley P. Slaughter, M.D.

11:00 a.m. ADNEXAL TUMORS OF THE SKIN
J. Leslie Smith, Jr., M.D.

11:30 a.m. ROLE OF RADIOTHERAPY IN THE TREATMENT OF BENIGN AND PRECANCEROUS LESIONS OF THE SKIN
Charles L. Martin, M.D.

12:00 noon Lunch

FRIDAY AFTERNOON, MAY 27

1:30 p.m. MALIGNANT SKIN NEOPLASMS—HISTOLOGIC DIFFERENTIATION AND BIOLOGIC BEHAVIOR
J. Leslie Smith, Jr., M.D.

2:00 p.m. PROBLEMS DEALING WITH THE PIGMENTED LESIONS INCLUDING MALIGNANT MELANOMA
George T. Pack, M.D.

2:30 p.m. BASAL CELL CARCINOMA AND PERSISTANT BASAL CELL CARCINOMA
Stephen R. Lewis, M.D.

3:00 p.m. Intermission

3:20 p.m. RADIOLOGICAL TREATMENT OF CANCER OF THE SKIN AND FACE
Charles L. Martin, M.D.

3:50 p.m. INDIVIDUAL VIEWS ON ABOVE SUBJECTS WITH DISCUSSION OR QUESTIONS AND ANSWERS FROM THE PANELISTS AND REGISTRANTS
Moderator: Stephen R. Lewis, M.D.
Participants: (All other guest lecturers)

5:20 p.m. End of Afternoon Session

7:00 p.m. SPONSORS SOCIAL HOUR AND BUFFET
Oklahoma Chapter of the American College of Surgeons
Oklahoma Association of Pathologists
Oklahoma Association of Radiologists

SATURDAY MORNING, MAY 28

8:45 a.m. MALIGNANT MELANOMA—HEAD AND NECK
George T. Pack, M.D.

9:30 a.m. INDICATIONS AND CONTRA-INDICATIONS OF ROENTGEN THERAPY IN CARCINOMA OF THE SKIN
Jose M. Sala, M.D.

10:00 a.m. INDICATIONS AND CONTRA-INDICATIONS FOR THE SURGICAL MANAGEMENT OF MALIGNANT SKIN TUMORS
Danley P. Slaughter, M.D.

10:30 a.m. Intermission

10:50 a.m. RADIOLOGIC TREATMENT OF SKIN CANCER OF THE NOSE, EAR AND ABOUT THE EYE
Charles L. Martin, M.D.

11:30 a.m. TECHNIQUES OF SURGICAL MANAGEMENT OF MALIGNANT SKIN TUMORS
Danley P. Slaughter, M.D.

12:10 p.m. Lunch

SATURDAY AFTERNOON, MAY 28

1:15 p.m. PATHOLOGIC CHANGES FOLLOWING TREATMENT OF MALIGNANCIES OF THE SKIN BY PERFUSION WITH P.A.M. DERIVATIVES
J. Leslie Smith, Jr., M.D.

1:45 p.m. MALIGNANT MELANOMA—TRUNK AND EXTREMITIES
George T. Pack, M.D.
2:30 p.m. GENERAL PLASTIC RECONSTRUCTIVE MEASURES
Stephen R. Lewis, M.D.
3:10 p.m. Intermission
3:30 p.m. INCIDENCE AND RADIOLOGIC TREATMENT OF LYMPH NODE METASTASIS
Jose M. Sala, M.D.
4:00 p.m. PANEL: TREATMENT OF CARCINOMA OF THE SKIN
Wrap-up questions and answers
Individual views of participants
Uncovered topics
Moderator: Danley P. Slaughter, M.D.
Participants: Stephen R. Lewis, M.D., Charles L. Martin, M.D., George T. Pack, M.D., Jose M. Sala, M.D.
5:00 p.m. J. Leslie Smith, Jr., M.D., with Oklahoma Association of Pathologists and registrant pathologists

Oklahoma's Reserve Hospital Is One Year Old

Oklahoma's first semi-mobile army reserve hospital, the 44th Evacuation Hospital, recently celebrated its first birthday. It was created by the Defense Department in April, 1959, as part of a reorganization of reserve forces.

Forty Men Needed

Colonel Hervey A. Foerster, M.D., Oklahoma City physician and hospital commander, pointed out his staff, which started with nineteen officers and eighty enlisted men, now includes thirty-eight officers, four nurses, three warrant officers and 116 enlisted men.

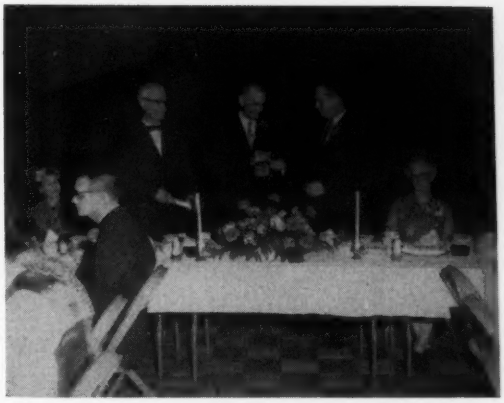
"However, the unit still needs about forty more enlisted men to be up to peacetime strength, and we can use some more doctors," the physician said. Physicians, he explained, may join the reserve unit even though they don't reside in Oklahoma City.

"We have one doctor who drives all the way from Ponca City for our drill sessions," Colonel Foerster said.

Summer Training Due

The 44th staff will take summer active training at Camp Hood, Texas, June 5-19. Half of the two week encampment will be spent in training at the post hospital. The second week will be spent in actual maneuvers, with simulated problems of battle conditions.

Wallis S. Ivy, M.D. Receives Double Honor



Shown receiving honors at the Stephens County Annual Doctors' Day Celebration is Wallis S. Ivy, M.D., (center), Duncan physician. Also pictured are (left to right) Mrs. Luther Roberts, Robert Dean Taylor, M.D., Luther Roberts, Doctor Ivy, Dwight Weedn, M.D. and Mrs. Ivy.

Wallis S. Ivy, M.D., Duncan physician, was twice honored when the Stephens County Medical Society held their Annual Doctors' Day celebration, March 29, 1960. A Fifty-Year Pin, commemorating his years of service to the medical profession was presented by the Oklahoma State Medical Association and, at the same time, a citation for outstanding accomplishment was pressented by the Duncan Chamber of Commerce.

Presentation of the Fifty-Year Pin was made by Dwight Weedn, M.D., President of the Stephens County Medical Society, and Luther P. Roberts of the Public Service Company presented the citation from the Chamber of Commerce.

Doctor Ivy is the oldest practicing physician from the standpoint of continuous service in Duncan and Stephens County. Coming to Oklahoma in 1915, Doctor Ivy established his practice in Marlow, moving to Duncan four years later. For the past 17 years, he has limited his practice to pediatrics.

AMA AHA Tighten Up On Foreign Grads

Hospitals employing graduates of foreign medical schools who fail to meet certain requirements by December 31 will face action by the American Hospital Association.

At that time, the AHA will cease listing hospitals which employ in patient-care situations foreign medical graduates who have not been certified by the Educational Council for Foreign Medical Graduates, Edwin L. Crosby, M.D., AHA director, said today.

Explanation of the ruling appears in a question-and-answer pamphlet now being mailed to all hospitals which are members of the AHA.

The AHA listing program provides a national census of hospitals that meet specific requirements. Listing is not intended to be a measure of quality or care, Doctor Crosby said. However, listing is a prerequisite for accreditation by the Joint Commission on Accreditation; thus if a hospital loses its listing, it automatically loses its accreditation.

The AHA ruling follows that of the American Medical Association, which has stated that it will withdraw approval of internships and residencies in hospital employing foreign graduates after July 1, unless the appointees meet one of the following requirements:

Possesses a full and unrestricted state license to practice; is in his final six months of training; possesses full or temporary certification from the Educational Council; or has been given a six-month appointment contingent on passing the September 21, 1960, examination by the Educational Council.

The Council was organized in 1957 for evaluating the qualifications of graduates of foreign medical schools. It is sponsored by the AHA, AMA, the Association of American Medical Colleges, and the Federation of State Medical Boards of the United States. The examination includes verification of educational credentials; an oral English test, and a written test of medical knowledge.

The Council was formed because of the number of graduates coming to the U.S. for advanced medical training and the difficulty in maintaining adequate information about foreign schools. Foreign graduates who are not in situations where they give direct care to the patient are exempt from certification. Graduates of Canadian and Puerto Rican medical schools are considered to be graduates of American schools.

"M.D. U.S.A." To Be Seen May 27

Oklahoma City's WKY-TV (Channel 4) will carry Smith, Kline and French Laboratories' latest program in the March of Medicine Series on Friday, May 27, from 9:00-10:00 p.m. Entitled "M.D. USA," the program is a "spectacular" in that camera crews were sent hopscotching over the face of America to film the story.

Traveling in jet airliner and on dogsled, the crews made on-the-spot reports from an isolated Alaskan village, from the delivery room of a small Louisiana hospital, from the great Navajo reservation in Arizona, from the office of a suburban Philadelphia physician, and from the rugged Door Peninsula of Wisconsin.

The story told is a simple but important one: Wherever Americans live, however they talk, dress or look, a doctor is on hand with skill, sympathy and understanding. And he is there because of dedication, the degree of which has not lessened through the years.

Members of the medical profession are encouraged to watch this excellent public relations presentation, and to invite their patients to do likewise.

ATTEND

THE OKLAHOMA WHITE HOUSE CONFERENCE ON AGING

JUNE 7 • 8 • 9, 1960

NORMAN, OKLAHOMA

Armed Forces Will Call Deferred Physicians

The Armed Forces will continue to require the services of most physicians liable for military service under the Universal Military Training and Service Act.

Lt. General Lewis B. Hershey, Director of Selective Service, issued this reminder to physicians when it became apparent recently that the Armed Forces would not call to active duty a small number of physicians in few specialties who had been deferred for residency training under the Armed Forces Reserve Medical Officer Commissioning and Residency Consideration Program.

All reserve officers deferred for residency in most specialties will be called.

Shortages exist and will continue in certain specialties and in the group of officers who have not specialized, according to information received by the Director of Selective Service from the office of Doctor Frank B. Berry, Assistant Secretary of Defense (Health and Medical).

The Selective Service Director urged physicians not to draw erroneous conclusions concerning the need of the Armed Forces for their services. If a substantial number of physicians, basing their decision on knowledge that a few reserve medical officers in a few specialties are not being called to active duty after residency, conclude they are not needed, existing shortages in the Armed Forces will be aggravated.

The Department of Defense has found it unnecessary to requisition physicians through the Selective Service System since early in 1957. This has been so only because sufficient numbers of physicians sought reserve commissions and thus made themselves available for call to active duty.

There is a continuing need for applications for the residency program, as well as for reserve commissions and active duty at the conclusion of internship, General Hershey stressed.

The temporary surplus in some specialties in the residency program is understandable. Estimates of needs must be made four or five years ahead. Other factors are revisions in Armed Forces strength, redistribution of troops, reorganization of the hospital system, specialists choosing a military career, and voluntary extension of duty tours by reserve officers.

Nuclear Society Will Meet in Colorado

The Seventh Annual Meeting of The Society of Nuclear Medicine will be held at the Stanley Hotel, Estes Park, Colorado, June 22-25, 1960. Henry H. Turner, M.D., Oklahoma City, is President of the group.

Over seventy speakers will present new scientific information covering every phase of research, medicine and surgery as it concerns the use of nuclear phenomena in the diagnosis and treatment of disease. Special emphasis will be given to the diagnosis and treatment of thyroid disease, therapeutic use of radioisotopes and "tools of the trade."

The First Annual Address of the Nuclear Pioneers Series will be delivered by Dr. Edward Teller of the University of California. This first address will be in honor of the late Doctor Ernest O. Lawrence.

The meeting is open to all physicians, veterinarians, nurses, physicists, technicians and other scientists working with, or interested in utilizing radioisotopes in the health field. There is a nonmember registration fee of $5.00. Registration forms and copies of the program may be secured by writing to Mr. Samuel N. Turiel, Administrator, The Society of Nuclear Medicine, 430 N. Michigan Avenue, Chicago 11, Illinois.

An Apology To Wesson Oil

The advertising index of the April issue credited the ad of the Wesson Oil and Snowdrift Sales Company to another advertiser.

Wesson Oil is a valued contributor to the *Journal* and the Editorial Staff wishes to take this opportunity to correct an unfortunate error.

Coming Meetings

UNIVERSITY OF OKLAHOMA MEDICAL CENTER
POSTGRADUATE PROGRAM*
Individual Postgraduate Courses

CARCINOMA OF THE SKIN—May 27-28. Surgery, Radiology, Pathology Conference.

SERIAL POSTGRADUATE COURSE
Postgraduate Division
Oklahoma City, Oklahoma
1959-1960

Wednesday Short Courses
3:30 to 8:30 p.m.

June 8 Practical Considerations of Neurological Problems

*Further information may be obtained from the Office of Postgraduate Education, University of Oklahoma School of Medicine, 801 N.E. 13th Street, Oklahoma City, Oklahoma.

POSTGRADUATE COURSE IN PEDIATRICS
The University of Colorado School of Medicine
September 1-6, 1960 **The Stanley Hotel**
Estes Park, Colorado

The Department of Pediatrics and the Office of Postgraduate Medical Education, University of Colorado School of Medicine will present a Course in Pediatrics at the Stanley Hotel, Estes Park, Colorado, September 1-6, 1960.

ROCKY MOUNTAIN CANCER CONFERENCE
July 20, 21, 1960 **Denver Hilton Hotel**
Denver, Colorado

The 14th Annual Rocky Mountain Cancer Conference will be held at the Denver Hilton Hotel in Denver, July 20, 21, 1960. Details may be obtained from the Rocky Mountain Cancer Conference, 835 Republic Building, Denver 2, Colorado.

SECOND ANNUAL
OREGON CANCER CONFERENCE
July 7-8, 1960 **Portland, Oregon**

The second Annual Oregon Cancer Conference will be held in Portland, July 7-8, 1960. A copy of the complete program may be obtained by writing to Roscoe K. Miller, Executive Secretary, Oregon State Medical Society, 2164 S. W. Park Place, Portland 5, Oregon.

6th INTERNATIONAL CONGRESS OF
INTERNAL MEDICINE
August 24-27, 1960 **Basle, Switzerland**

The 6th International Congress of Internal Medicine will convene in Basle, Switzerland, August 24-27, 1960. Simultaneous translation for the principal speakers will be given in German, French and English. Programs and registration forms are available from the 6th International Congress of Internal Medicine, Steinentorstrasse 13, Basle 10, Switzerland.

Deaths

ALLISON T. GRAHAM, M.D.

1891-1960

Allison T. Graham, M.D., an Oklahoma City physician since 1920, died March 28, 1960.

A native of Eastman, Mississippi, Doctor Graham graduated from Memphis Hospital Medical College of Tennessee in 1913. He served two years as a major in the Army Medical Corps during World War I.

An Honorary-Life Membership in the Oklahoma State Medical Association for Doctor Graham was pending at the time of his death.

JAMES HAROLD PARKER, M.D.

1886-1960

James Harold Parker, M.D., retired Oklahoma City psychiatrist and veteran of 26 years' service with the federal government, died April 21, 1960 in Oklahoma City.

A native of Berryman, Missouri, Doctor Parker graduated from the University of Louisville School of Medicine in 1910. Before joining the Veterans Administration, Doctor Parker served as superintendent at state mental hospitals in Farmington and St. Joseph, Missouri.

His career with the Veterans Administration began in 1930 at Alexandria, Louisiana. He later served at Veterans Hospitals in Waco, Texas, Sheridan, Wyoming and Muskogee, Oklahoma before coming to Oklahoma City.

Auxiliary News

Finale

Our Oklahoma State Convention held May 1 to 4 in Oklahoma City provided an enthusiastic recapitulation of the past year's activities, plus a forward look to the coming year under the direction of new officers. We sincerely thank Mrs. Clifford M. Bassett, past State President, and all of her co-workers. We warmly welcome our new President, Mrs. Virgil Ray Forester, our new officers and chairmen, as they initiate plans for the coming year.

On to A.M.A.

As our own convention concludes this phase of our county activities, so the 1960 Woman's Auxiliary to the American Medical Association climaxes the composite work of all of our state auxiliaries. This year the convention will be held June 13 to 16 at Miami Beach, Florida.

Hotel Deauville will be headquarters for the pre-convention meetings which start June 11. Oklahoma will be represented by Mrs. Bassett and Mrs. Forester at these meetings. Mrs. Neil Woodward, National Civil Defense Chairman, will present a skit, "Operation Home Preparedness" during the morning session of the regular convention, June 14.

The following day Mrs. Frank Gastineau, out-going National President, will present the gavel to our new President, Mrs. William Mackersie. Mrs. Richard F. Stover of Miami, Chairman for the 37th Annual Convention, invites all members to participate in a stream-lined convention program, with ample free time allowed for sight-seeing and shopping.

Bring Your Family

From the advance bulletin: "Cabana parties, sight-seeing cruises—even ice-skating —are included in the entertainment planned for elementary and teen-age children attending the AMA convention with their parents. The Deauville boasts the only artificial ice-skating rink on the famous Gold Coast. Entertainment for the young people will get under way Monday, June 13, with a boat ride which takes them through the beautiful man-made islands. Two trips—one for the elementary group, one for the teen-age—will be made. A pool and patio supper party takes place Monday evening from 6 to 10:30 for the teen-agers, on the beach and around the Deauville cabanas."

Tours of Miami, Miami Beach and points of interest in Dade County will be available on Tuesday, Mrs. Stover announces. She adds that "children of elementary school age will have supervision, so that if mother is in a committee meeting, she won't be worrying about her child."

Lyla Dix, Publicity Chairman for the Convention, has helpfully issued the following information: Miami in June promises highs of 86 degrees and minimums of 77 degrees, emphasizing a choice of packing: Come with empty bags and take advantage of the sales of resort clothes. Or, if you prefer to "bring your own," keep in mind that Miami Beach is "casual and sophisticated, but not careless." Shorts, slacks and beach attire are the order of the day and may be worn, in addition to the beach and sports events, in the lower lobby and the coffee shop of the Deauville; not in the main dining room or the main lobby. Linens, cottons and comfortable summer things are stressed. Jackets and sweaters are musts for air-conditioned meeting rooms.

Our general invitation to Miami Beach and AMA is: Come—Bring the Family—and Have a Wonderful Time!

25 YEARS AGO

Articles published in *The Journal* of the Oklahoma State Medical Association, May, 1935.

THE USE OF DILAUDID IN GENERAL PRACTICE

Clifford M. Bassett, M.D., Cushing

The drug dilaudid is a morphine derivative, dihydromorphine hydrochloride, a rearrangement of the morphine molecule. This change in chemical structure of the morphine molecule increases the analgesic effect about five times, appears to remove the constipating effect and also seems to eliminate much of the euphoric effect of morphine. My observation has shown that the nauseating and emitic effect of morphine are almost entirely absent. With one or two patients I observed slight dizziness and confusion, but this was transient, lasting but a few minutes.

Dilaudid, in general practice, gives the physician a drug that can be employed in many varied conditions to bring relief from pain. It is a powerful analgesic, with a prompt and definite action. Following a specific dose, a corresponding certain degree of analgesia may be expected. I have given patients morphine in ¼ grain doses only to find it necessary to repeat the dose in 30 to 40 minutes; with dilaudid I have not encountered a case that either 1/32 or 1/20 of a grain did not give complete and persistent relief. I have not found it necessary to give large doses, as the effect of dilaudid persisted for some time following its administration. In the post-operative cases many of the patients go from six to eight hours before requiring further analgesic medication.

The relaxing properties are also apparent in the post-operative period as shown by the infrequent occurrence of urination retention, requiring catheterization. It was not necessary to catheterize during the post-operative course when dilaudid was used for pain. Those patients for which catheterization was advised for a time following the operation, as for example, after perineorrhaphy, were able to void easily when allowed to do so. No doubt in a larger series it might be necessary to occasionally catheterize a patient post-operatively but if the necessity for this procedure is reduced to a minimum, that factor alone should invite the universal adoption of dilaudid over any other opiate in post-operative pain.

I have also used dilaudid as a cough sedative with good results. It exhibits a sedative effect similar to heroin and in very small doses. I have used as little as 1/20 to 1/10 grain in one ounce of vehicle. It does not inhibit secretions, induce constipation, nor do the patients complain of drowsiness.

One factor which makes the drug pleasant to work with is its solubility. The time consumed in preparing hypodermic medication is greatly reduced, and this, plus rapidity of action of the drug, insures relief to the suffering patients in the shortest possible time.

Have You Heard?

PAUL KERNEK, M.D., Holdenville, was recently appointed by Governor J. Howard Edmondson to fill an unexpired term on the State Board of Health. The vacancy occurred when M. L. Whitney, M.D., Okemah, resigned.

W. D. ANDERSON, M.D., M. E. GORDON, M.D., O. U. HOLT, M.D., M. R. JENNINGS, M.D., and ROBERT M. STOVER, M.D., of Claremore, have set up a scholarship for a student nurse each year for the next three years. The girls selected by the physicians may attend any accredited nurses' training school. Following graduation, the nurses will be expected to spend at least one year at the Claremore Health Center, providing there is an opening at that time.

PHILLIP SHEPPARD, M.D., Tulsa, will be associated with Eugene Bell, M.D., in the Bell Clinic in Tishomingo after July 1. Doctor Sheppard graduated from the University of Oklahoma School of Medicine before taking his internship at St. John's Hospital in Tulsa.

RALPH BULLER, M.D., Lafayette, Louisiana, will establish his practice in Hydro after September 15. Doctor Buller, a graduate of the University of Oklahoma School of Medicine in 1956, served two years in the Air Force before taking a residency at the Charity Hospital of Louisiana.

PHYSICIAN PLACEMENT

Dermatology

Gordon Harold Ekblad, M.D., Field Medical Service School, Camp Pendleton, California, 53, married, University of Minnesota, 1930, available January 1960.

Lealand L. Clark, M.D., 200 1st St., S.W., Rochester, Minnesota; age 28; married; Columbia University College Physicians and Surgeons 1956; Board eligible July 1960; Fellows' Assoc., Mayo Foundation; Military service will be completed Sept. 1962; desires group or associate practice; available July 1960.

Joseph William Pidgeon, M.D., 5333 Littlebow Road, Rolling Hills, California; age 41; married; George Washington University 1951; Board eligible June 1960; Active Air Force Reserves; available July 1960.

General Practice

Johnny Bill Delashaw, U.S.P.H.S. Hospital, Wyman Park Drive and 31st Street, Baltimore 11, Maryland, age 27, married, University of Texas Medical Branch, 1959, available July 1960.

Robert G. Bissell, M.D., 143 S. Wheeling, Tulsa, Oklahoma, age 28, married; University of Oklahoma School of Medicine, 1959; no military obligations; available July 1, 1960.

Robert Goodman, M.D., 63 Old Gate Lane, Powers Lake, North Dakota; age 56; married; University of Manitoba, 1930; no military obligations; available anytime 1960.

Richard Fred Harper, M.D., Conway Memorial Hospital, Monroe, Louisiana; age 28, married; Oklahoma University, 1956; available July 1960; prefer associate practice.

Sherman Allen Hope, M.D., 1105 Yale Ave., Panama City, Florida, PO 3-6656, age 27, married, University of Oklahoma School of Medicine, 1957, available July 1960.

Internal Medicine

Richard I. Hochman, M.D., 37, Badger Road, Annapolis, Maryland, 31, married, New York University, 1952, available October 1, 1960.

Edward John Hertko, M.D., 2117 S. 3rd Ave., Maywood, Illinois; age 30; married; University of Illinois, 1954; no military obligations; available October 1960.

Joseph Chester Maternowski, M.D., 319 Highlake, Ann Arbor, Michigan; age 35; married; St. Louis University, 1953; eligible board of Internal Medicine & Allergy; veteran; specialty, Internal Medicine & Allergy; available July 1, 1960.

Locum Tenens

Harold W. Calhoon, M.D., Wesley Hospital, Oklahoma City. One year residency in Internal Medicine. Available July 1 to September 15th, 1960.

Arnold Giesbrecht, M.D., Hallock, Minnesota, age 34, married, graduate Winnipeg, Manitoba, 1957, prefers suburban or locality close to cities.

James D. Green, M.D., second year resident in Internal Medicine at St. John's Hospital, Tulsa, desires two weeks' tenure between now and July 1. Write to St. John's or call RIverside 3-3059.

(Name on Request), O.U. graduate 1956; M.D. from Washington University School of Medicine 1959; desires locum tenen in the Tulsa area from July 1, 1960 until middle of September, 1960. Address inquiries to Key H, The Journal, Oklahoma State Medical Association, P.O. Box 9696, Oklahoma City, Oklahoma.

Charles L. Maimbourg, M.D., Campus Apartments No. 5, Elf Street, Durham, North Carolina; Oklahoma University School of Medicine 1958; desires General Practice and/or Anesthesia during first two or three weeks of July 1960.

Russell M. Preston, M.D., 476 San Juan, Oak Harbor, Washington, desires six month's work in General Practice between time of separation from military service to beginning of residency training, January-July, 1960.

Obstetrics and Gynecology

Edmond Michael Brophy, M.D., 1823 Portsmouth, Westchester Illinois; married; University of Illinois, 1946; Board eligible upon completion of practice requirements; no military obligations; available July, 1960.

William Edgar Carlisle, M.D., 634 E. Patton Ave., Montgomery, Alabama; age 29; married; Tulane University School of Medicine 1953; Jr. Fellow American College of Ob-Gyn; interested in associate or group practice; available July 1960.

Robert Russell Fahringer, M.D., P.O. Box 148, Danville, Pennsylvania; age 35; married; Jefferson Medical College of Philadelphia, 1953; inactive military status, USNR; prefers full or part-time teaching; available February 1960.

Joseph William Herbert, M.D., 2701 N. Azelea St., Victoria, Texas; age 40; married; Southwestern Medical School, 1945; Fellow American College of Ob-Gyn; desires associate or solo practice; no military obligations; available March 1960.

David H. Holmes, M.D., 1017 Grovena Drive, St. Louis, Missouri, 37, married, Washington University, St. Louis, Veteran, available July 1, 1960.

Gerald R. Keilson, M.D., Medical Arts Building, Dallas, Texas, age 31, married, University of Texas, 1953, board qualified, veteran, available in July 1960.

Nejdat Mulla, M.D., 1110 Belmont Avenue, Youngstown, Ohio, age 36, married, University of Geneva, Switzerland, 1952, American College of OB-GYN, not eligible military service, available July 1, 1960.

Oklahoma physician; age 35; married; Medical College of Georgia, 1954; 3 years residency training Ob-Gyn; veteran; available in 30 days. Write Key "I", Oklahoma State Medical Association, P.O. Box 9696, Shartel Station, Oklahoma City, Oklahoma.

Harold G. Ray, M.D., 212 Darien Place, Box 503, Balboa Heights, Canal Zone, age 28, married, University Arkansas School of Medicine, 1955, now in active reserve, available July 1, 1960.

Harold E. Reid, M.D., 519 N. Lincoln St., Stanton, Michigan; age 42; married; University of Michigan, 1942; OB-GYN, also interested in industrial; available February 1960.

Juan C. Ruiz, M.D., 350 Park Ave., Lexington, Kentucky; age 36; married; University of San Marcos Medical School 1952; no military obligations; available July 1, 1960.

Pediatrics

H. M. McClintock, M.D., 5712 St. John St., Kansas City, Missouri, 29, married, Baylor University, 1955, veteran, available December 1960.

Ophthalmology

Howard A. Dinsdale, M.D., 4624 Briarfield Road, Columbia, South Carolina; age 29; married; University of Nebraska 1954; Board Certified; available October 11, 1960.

Ira H. Kaufman, 75 S. Middle Neck Road, Great Neck, New York; age 31; married; Cornell University 1953; Board certified; desires group or associate practice; available summer 1960.

Orthopedics

Newsom Stool, M.D., c/o May Clinic, Rochester, Minnesota; age 30; married; Baylor University 19[illegible]; Board eligible; available July 1960.

Surgery

(Name on Request) 32 years old, married, Tulane, 1952, veteran, board eligible.

Clarence I. Britt, M.D., 1650 Neil Avenue, Apt 15, Columbus, Ohio; age 32; married; Ohio University College of Medicine, 1951; American Board of Surgery 1959; eligible American Board of Thoracic Surgery, 1960; inactive reserve; available July 1960.

Delbert H. McGinnis, M.D., Box 75, Clinton-Sherman AFB, Oklahoma; age 28; married; end military obligation July 3, 1960; interested in general practice; available July 4, 1960.

Duane M. Clement, M.D., 310 Bates, Boulder, Colorado; age 39; married; University of Michigan 1944; Board certified; member F. A. Coller Surgical Society; desires group or associate practice; available April 1960.

Alice F. Gambill, M.D., 1601 Clover Lane, Fort Worth, Texas; age 36; married; Oklahoma University School of Medicine 1949; member AAGP; desires general or group practice; available May 1960.

Donal Wray Steph, M.D., 8519 Craighill, Dallas, Texas; age 30; married; Southwestern Medical School 1953; board eligible July 1960; available July 1960.

Clinton K. Higgins, M.D., 215 Bacon Ave., Naval Base, Norfolk, Virginia; age 62; married; Washington University 1927; Board Certified; desires administration, college health physician, group association; available May 1960.

Urology

Alex Grossman, M.D., V.A. Center, Temple, Texas, 42, married, University of Texas, 1951, board certified, veteran, available now.

John A. Malley, M.D., 3404 Sheffield Ave., Los Angeles, California; age 32; married; Marquette University 1955; Board certified; no military obligations; available July 1, 1960.